

AMERICAN JOURNAL OF OPHTHALMOLOGY

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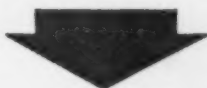
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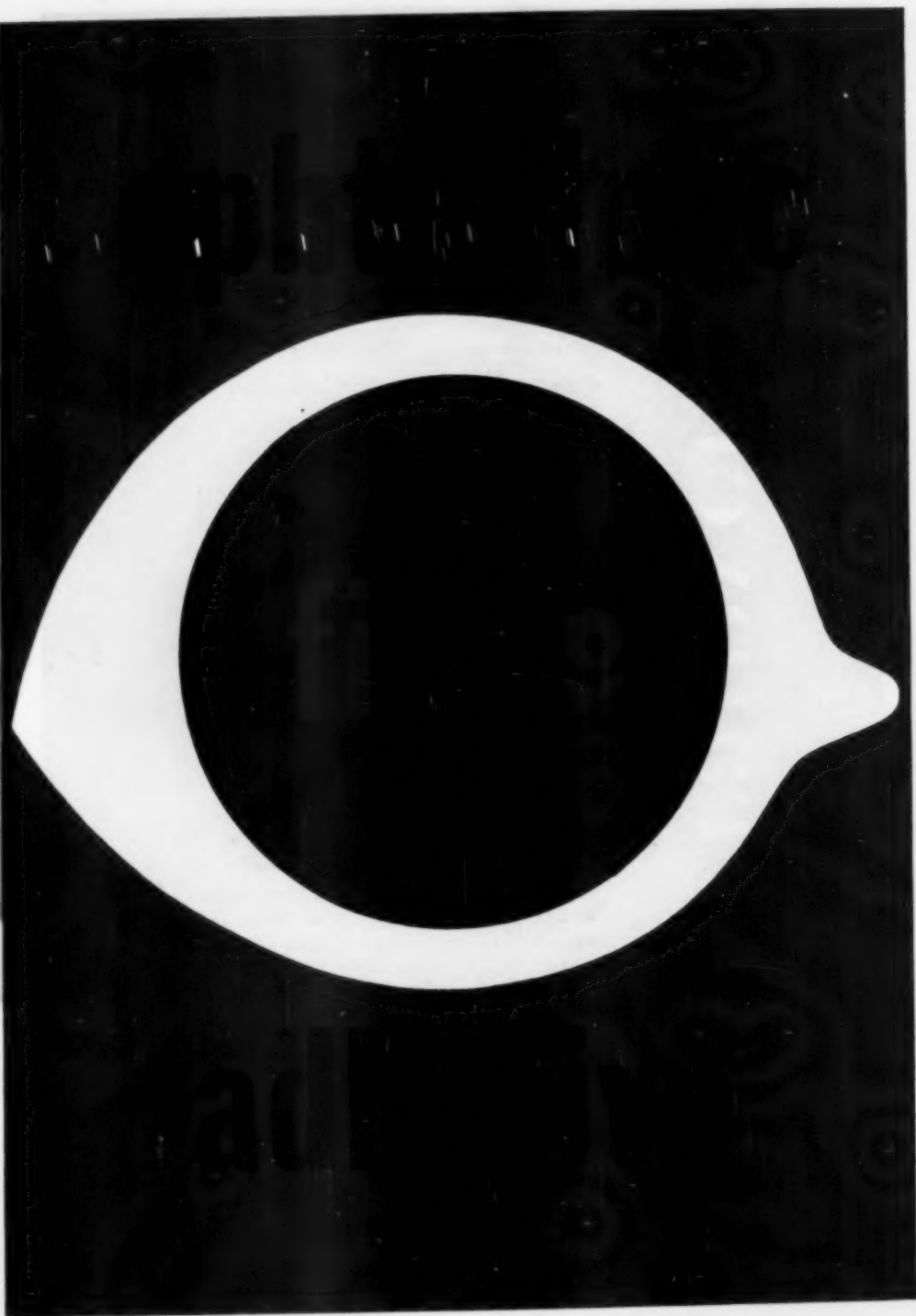


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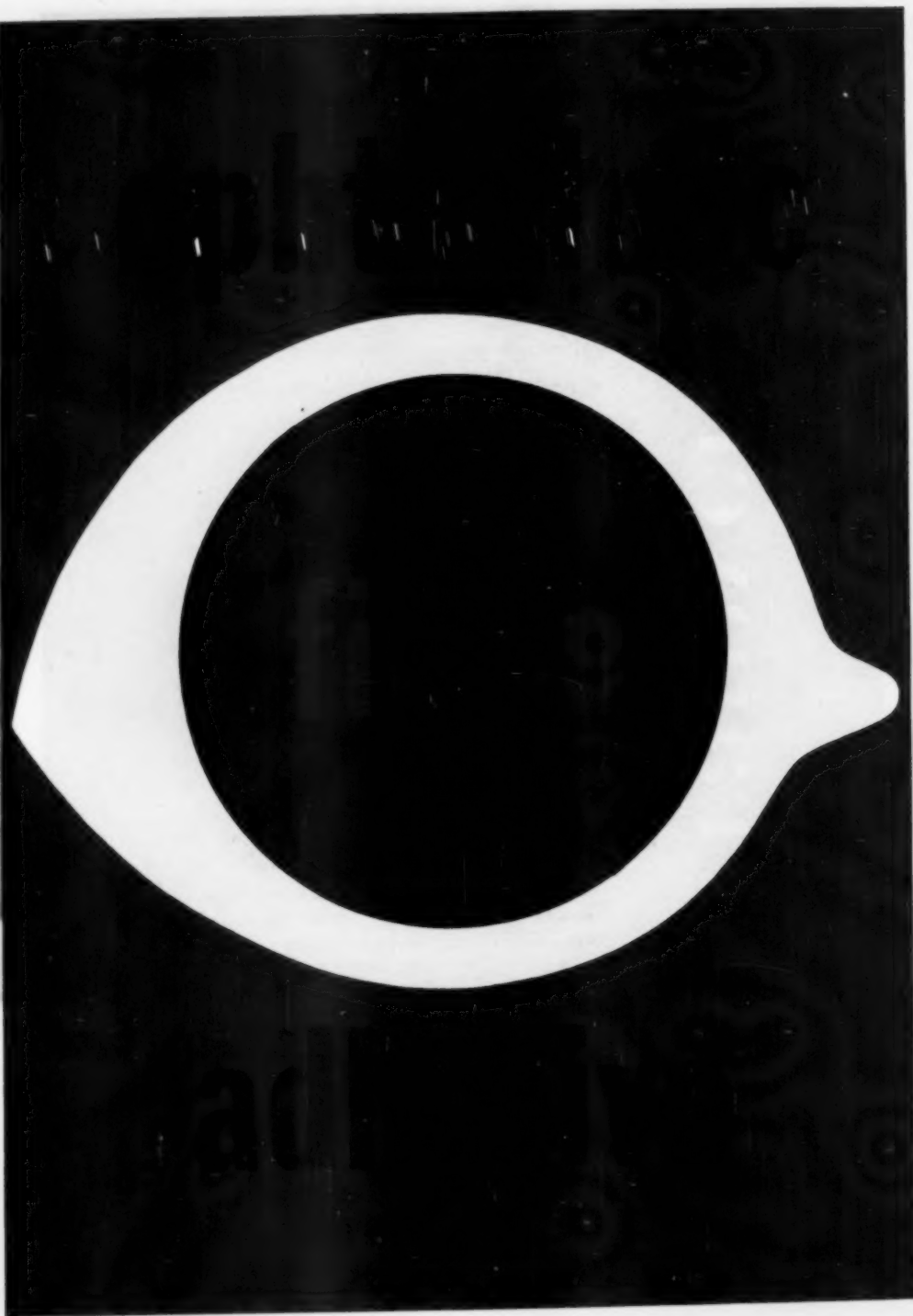
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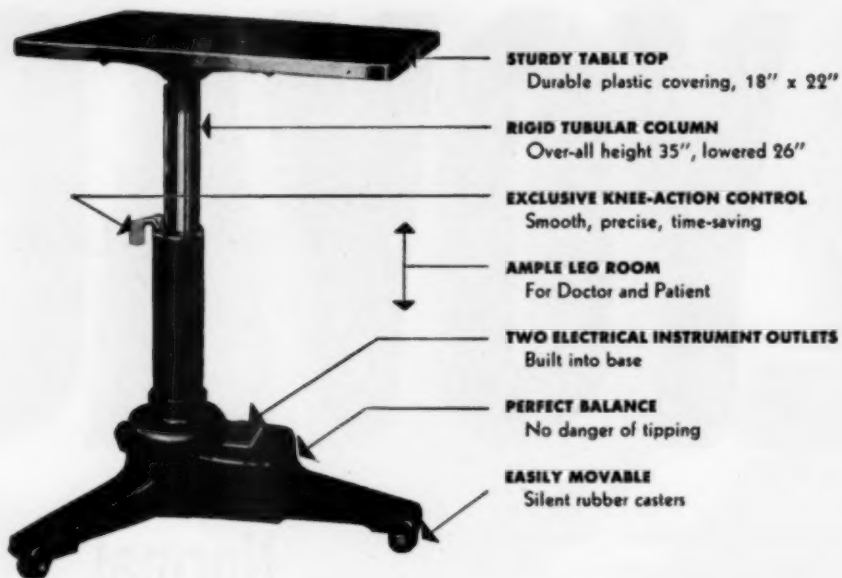
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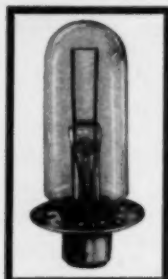
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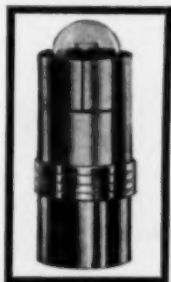
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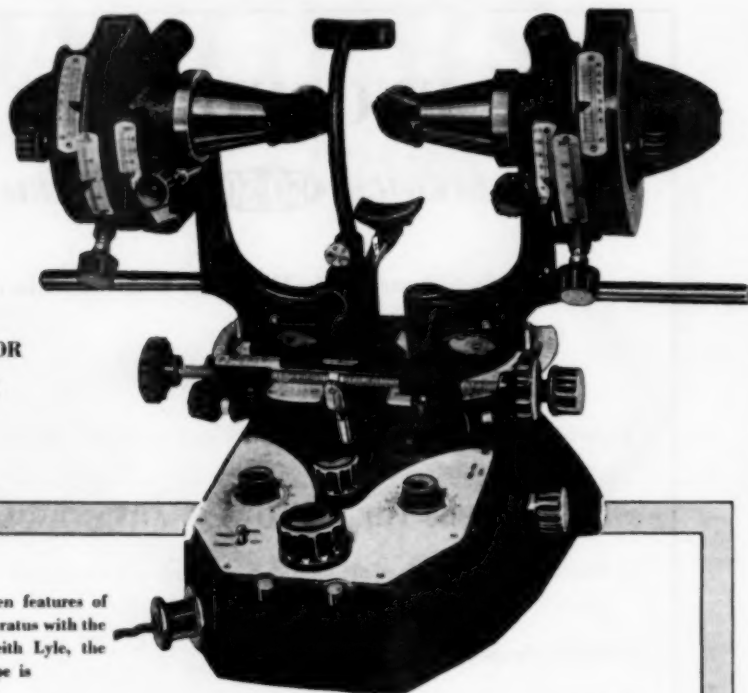
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* Mims, Jr., S. L., *Arch. Ophth.* 46: 664-665 (Dec.) 1951.

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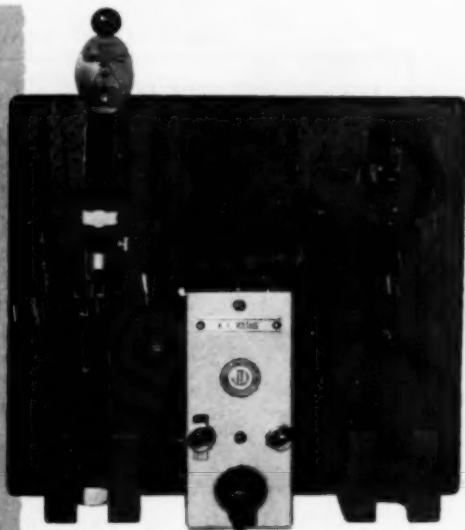
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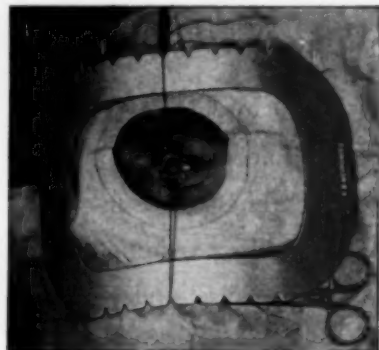
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ABSTRACTS

Uvea, sympathetic disease, aqueous; Glaucoma and ocular tension; Crystalline lens; Retina and vitreous; Neuro-ophthalmology; Eyeball, orbit, sinuses; Eyelids, lacrimal apparatus; Tumors; Injuries; Systemic disease and parasites; Congenital deformities, heredity; Hygiene, sociology, education and history	732
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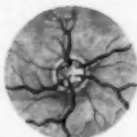
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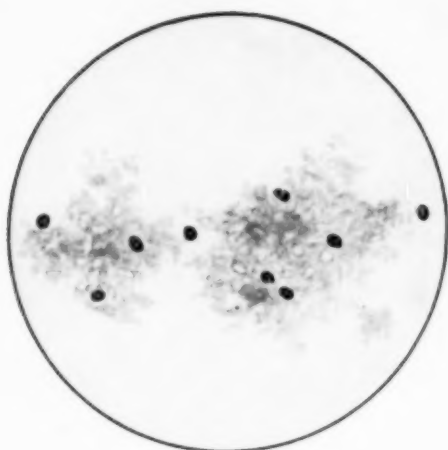


FIG. 1



FIG. 2

FIGS. 1 AND 2 (POLEFF). (FIG. 1) INCLUSION BODIES OF TRACHOMA UNDER SLIGHT MAGNIFICATION (POLEFF STAIN).
(FIG. 2) INCLUSION BODIES OF TRACHOMA, SHOWING ELEMENTARY AND INITIAL BODY FORMS (POLEFF STAIN, X1,000).

SIMPLE AND RAPID CONTRAST STAINING OF TRACHOMA BODIES*

L. POLEFF, M.D.

Rabat, Morocco

The etiologic role of the trachoma bodies, discovered in 1907 by Prowazek and Halberstaedter (Prowazek-Halberstaedter inclusion bodies), and whose living nature has been shown by cultures in vitro and in incubated hen eggs (Poleff, 1936; Cuenod and Nataf, 1938; Macchiavello, 1941), seems now to have been proved beyond any possible doubt.¹

These formations of the rickettsioid-corpuscular type reveal, both in the conjunctival cells invaded by them and in the cultures in appropriate tissues, the various stages of development (cycle of evolution or different forms of resistance) of an ultravirus which, according to its morphobiologic characteristics belongs to the pararickettsia group: *Pararickettsia trachomatis* (Prowazek and Halberstaedter, 1907; Poleff²).

The principal evolutionary forms of this ultravirus (initial bodies and elementary corpuscles) are differentiated by their size and their color affinities. The initial bodies are basophils and the elementary corpuscles in their pure state are acidophils. In consequence, with the classical Giemsa stain, the former give dark-blue and the latter red. However, owing to the various transitional forms between the two principal stadia just named, it is not always easy to identify in a clear way these forms on a color pattern.

In addition from a morphologic point of view, since the trachoma bodies and in particular the elementary corpuscles, by their

typical intracellular seating and their general aspect, present all the characteristics of infragerms, the viroscopic examination in a case of trachoma necessitates a far from negligible study in order to differentiate this multiform rickettsioid virus from the numerous multicolored granulations which one always comes across in trachomatous scrapings treated by Giemsa stain.

When one recalls that even trachoma experts must examine many thousands of epithelial cells before giving a definite verdict as to the presence of trachoma bodies, one realizes the number of hours it sometimes takes to make a viroscopic examination in a single case in which trachoma is suspected.

Every trachomatologist, practitioner as well as research worker, would like to have a simple staining method which permits a rapid and sure identification of trachoma bodies, for none of the methods employed in general virology seem to have the same characteristics in cases of trachoma.

Among these methods that of Macchiavello, now of general use for the rickettsia, seems to be of particular interest. I have used it at the Institut Pasteur at Paris in the laboratory of Paul Giroud whose work in this field is widely known. I was convinced that the trachoma bodies are not stained in a typical way—to a ruby red—with Macchiavello's method (that is, basic fuchsin, citric acid, and methylene blue *rapidly applied*).

In pursuing this line of investigation in Morocco, and in practicing successively the different phases of this staining method, I noticed that the application of fuchsin alone,

* From the Centre d'Ophthalmologie et de Trachomatologie Experimentale, Maréchal Lyautey.

upon which Macchiavello's method was originally based, does not permit the distinguishing of trachoma bodies.

A better, though not very satisfactory, result is given by staining with methylene blue untreated by citric acid.* But citric acid, used previously alone or in mixture with methylene blue and *for a longer time*, gives a perfect contrast staining. Intracellular inclusions and free elementary corpuscles stain in red with a violet tinge on a blue background distinctly differentiated and traceable even after only slight magnification (figs. 1 and 2).

It seems then that methylene blue treated with citric acid is capable of modifying the stain in the presence of trachoma bodies which thus become stained distinctively and clearly from the rest of the preparation. This property of methylene blue to change color under certain chemical conditions is well known (Codex, p. 120, 1937).

In order to study this characteristic in relation to trachoma bodies I made a series of experiments controlled by different chemicals (mineral and organic acids, alcohol acid, alcohol, and so forth) and came to the conclusion that the modification of the staining is due rather to the alcoholic function than to the acid function of the citric acid. In fact, I obtained the same staining by adding ammonium citrate to the methylene blue instead of citric acid; that is to say that, when the acid function of the methylene blue was stopped, the alcoholic function was able to operate.

This observation, very important to examinations for trachoma, may also be useful in general virology.

My staining technique is thus reduced to a single operation and consists of staining for three minutes the scrapings which have been fixed by flame with a solution of 1.0 gr.

methylene blue and 0.50 gr. of citric acid in 100 cc. distilled water. The citric acid may be replaced by the citrate of ammonium or by acetic or lactic acids.

The method here described differs, therefore, from that of Macchiavello both in its principal agent (methylene blue instead of fuchsin) as well as in its technique. I call it "staining by citrate methylene blue" and consider it, for the moment, to be the most practical method for rapid diagnosis of the trachoma bodies.^{3,4}

Up to the present I have applied it successfully in more than a 1,500 control and trachoma scrapings collected with an epidemiologic aim—in particular, for the tracking down of trachoma-body carriers among the Moroccan school-children.⁵

This research shows the following results:

Out of 219 certain cases of trachoma, 94.5 percent were bearers of trachoma bodies. Among 281 apparently healthy subjects or doubtful carriers 42.3 percent were revealed to be carriers of proved trachoma bodies.

Thus for the first time and by direct viroscopic examination on a large scale, the existence of carriers of trachoma infection among apparently healthy individuals and the presence of infection in patients with no apparent symptoms were objectively proved.

The establishment of this fact is of prime importance to the prophylaxis of trachoma, not only on an individual level but also on a social and international level.

SUMMARY

I propose a new staining method for trachoma bodies called "staining with citrate methylene blue."

TECHNIQUE

1. Fixation by flame.
2. Stain for three minutes in a mixture of 1.0 gr. of methylene blue and of 0.50 gr. of citric acid in 100 cc. of distilled water.
3. Rinse with ordinary water.

* The best results were obtained with American methylene blue (product of Chemo-Puro Manufacturing Corporation, New York).

RESULTS OBTAINED

Trachoma bodies stained a vivid violet-red on a clear blue background (figs. 1 and 2).

The advantages of the technique are rapidity and extreme simplicity, as well as clear differentiation and perfect contrast of staining.

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EFFECTIVE AND SAFE RADIATION OF THE ANTERIOR SEGMENT OF THE EYE*

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Buffalo, New York

There are several modalities of radiation which are at present available to the ophthalmologist for the treatment of disease of the anterior segment of the eye. It is the purpose of this paper to comment upon the physical aspects of these various sources and also to include some personal experiences in the handling of several of them.

The use of radium for treatment of eye disease, including deeply situated lesions (where gamma radiation is required), is not new. More recently well-founded claims have been advanced for the efficacy of beta irradiation of the anterior segment.¹ It is necessary to emphasize that depth of penetration varies widely with various sources of radiation, and that consequently data on depth dosage presented in this paper can be used to select wisely sources of radiation for differently situated lesions.

Appreciable radiation dosage is required to treat vascular lesions of the cornea and conjunctiva; here, in order to avoid radiation cataract, it is important and feasible to select a source which will not irradiate as deeply as four mm., the approximate distance of the lens from the surface of the human eye.²

It is possible that the important investiga-

tion being undertaken at Northwestern University Medical School on the site of tissue involved in the production of radiation cataract will throw further light on this aspect of the criteria of safety of beta irradiation of the eye. For the present, and from the practical standpoint, the view expressed above appears adequate.

At the same time, since both alpha rays and the variety or spectrum of beta rays secured from radium-D are filtered out by extremely small distances, it is frequently important to choose a source that will deliver therapeutic radiation within the substance of the cornea, or on its inner surface. Furthermore, the radiating element itself cannot be applied at precise contact to the cornea; it can be held no closer to the cornea than the thickness of the inert metal on the face of the plaque plus the varying distance of the curved cornea from the usually flat plaque surface.

In other words, the aim, in treating the anterior segment, should be to attain adequate delivery of radiation in the tissue at the various depths of vascularization or other lesion without penetration deep enough to injure the lens. Data herewith indicate that this can be accomplished.

The following modalities will be consid-

* From the Millard Fillmore Hospital.

ered: low-voltage X rays (including the so-called contact therapy generator), Grenz rays, beta radiation from a radium plaque, from radon, from a radioactive isotope of strontium, and from a "radium-D" plaque, all used to treat vascular and lymphoid lesions and scars of the anterior region of the eye.

Radiation such as X rays and radiations from radium and its disintegration products have been a modality of treatment of certain human diseases since their discovery approximately 50 years ago. The degree of biologic responses to these sources of radiation may be said to be the result of three factors:

1. The total dose received by all parts of the tissue irradiated.
2. The time during which the exposure was made.
3. The number and frequency of radiation treatments.

The degree of penetration of X rays (depth dose) is a function of the wavelength of radiation, the distance from the source of radiation, and the size of the area treated. Filters may be introduced to change the wavelength distribution by absorbing the long wavelength components, thus making the X-ray beam more penetrating.

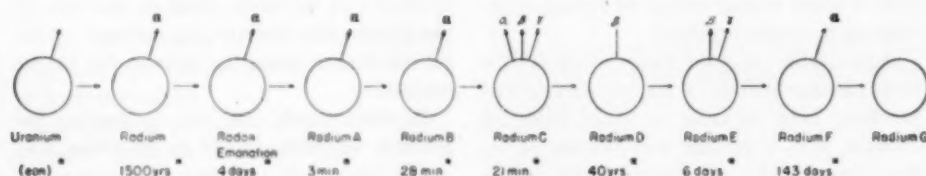
Similarly, the depth dose from radium contains beta particles with variable velocities and gamma rays of varying wavelengths. Radium also emits alpha particles which are biologically active but these particles are so large that they do not travel more than the

thickness of a sheet of paper and are filtered out in the applicators which we use by the thickness of the Monel metal on the face of the applicator. Since beta particles are also material and have weight, they do not travel far and are so effectively filtered out within the distance of a few millimeters that, by selecting the source of the beta irradiation, the depth of tissue responses can be very accurately controlled.

Gamma rays are electromagnetic radiations and are a part of the spectrum which includes visible light. Gamma rays, like other electromagnetic waves, travel far, and when platinum instead of Monel metal is used to face the radium of the plaque most of the beta rays are filtered out. The resulting preponderance of gamma can cause intraocular damage.

Radium rays as ordinarily used for the treatment of cancer are indeed rather heavily filtered, so that the relatively nonpenetrating beta particles which comprise over 98 percent of the total emission from radium will not burn or overtreat nearby tissues. Such a filtered radium applicator, with an effective dosage of less than two percent of its total biologically active radiations, is ordinarily applied for hours at a time and provides so much depth of penetration that with it the lens of the eye might be damaged before a superficial lesion could be adequately treated.

On the other hand, an "unfiltered" radium plaque faced with Monel metal which does not obstruct the passage of either beta or



* ESTIMATED PERIOD OF TIME IN WHICH HALF OF ANY SAMPLE IS TRANSFORMED INTO THE NEXT SUBSTANCE IN THE SERIES.

Fig. 1 (Hague). Radioactive disintegration from radium through radium E.

TABLE 1

THIS TABLE SHOWS THE GREATER VELOCITY OF BETA PARTICLES FROM RADIUM (WHICH INCLUDES IN EFFECT RADIUM-B AND C), THAN FROM RADIUM-D

Ra	Rn	RaA	RaB	RaC	RaD	RaE	RaF	RaG	Half-life Period
1696 yr.	385 days	3.0 min.	26.8 min.	19.5 min.	16.5 yr.	5.0 days	136 days		
Velocity of B particles where light equals 1			0.36	0.786	0.33	Velocity			
			0.41	0.862	0.39				
			0.63	0.949					
			0.70	0.957					
			0.74						

gamma radiation to any extent gives off over 58 percent of radiation which penetrates only a few millimeters; and in the brief period of time necessary to obtain therapeutic results with the high proportion of beta radiation from unfiltered radium, the more deeply penetrating gamma content of the dose may be ignored.

This statement is confirmed by the data accompanying this paper and by nine years' personal experience with the application of unfiltered radium to the eye. During this period I have not been aware of observing any damage to the lens, and it is my impression from a personal review of literature that so far as can be determined from data presented, ocular damage resulted only from incautious or heavy dosage of gamma.

In considering the relative depth of penetration of radium and radium-D, let us refer to the diagram (fig. 1) showing the degeneration series of radium. The average energies of beta rays omitted by radium-B and C (which give off the effective radiation from radium itself) are appreciably greater than the energies from radium-D and E. This is evident in the depth dose curves which we have measured and calculated.

(Radium-D and E are constantly accumulating in any radium applicator but because of the long life of radium-D, the number of these atoms exploding per second is very small and their contribution is negligible in the beta radiation from a radium applicator, where the beta source is primarily from radium-B and C, whose life is virtually measured in minutes.)

Furthermore, referring to Table 1, it will be seen that the velocity of the beta rays virtually from radium (radium-B and C) is greater, and consequently the penetration is deeper, than from radium-D (+E).

The various rays from radium ionize gases, effect photographic plates, modify living tissue, and produce other rather striking effects. Most of these effects have been used to measure radiation. Methods of measurement include certain chemical reactions which Roentgen himself referred to, fluorescence, electrical resistance, estimation of erythema changes in skin, measurement of heat produced by the absorption of radiation in metals, measuring of ionization effect, and photography.

For the measurement of a flat plaque of radium or radium-D, where the active material is as flat a layer as possible, the photographic method is probably the best. Using this method, and as well a biologic estimation, that of comparing the erythema reactions of skin, we find that both radium and radium-D do not produce enough penetrating radiation to injure the lens of the eye with anywhere near the doses that easily could or would be employed. Dosage is limited by the fact that beta irradiation, more or less confined to a surface, will produce severe burns with a good deal less dosage than would be necessary to deliver effective gamma irradiation.

The depth dose determinations* were

* The photographic calibrations in this paper were made by Dr. Melvin Reinhard, Roswell Park Institute, Buffalo, New York.

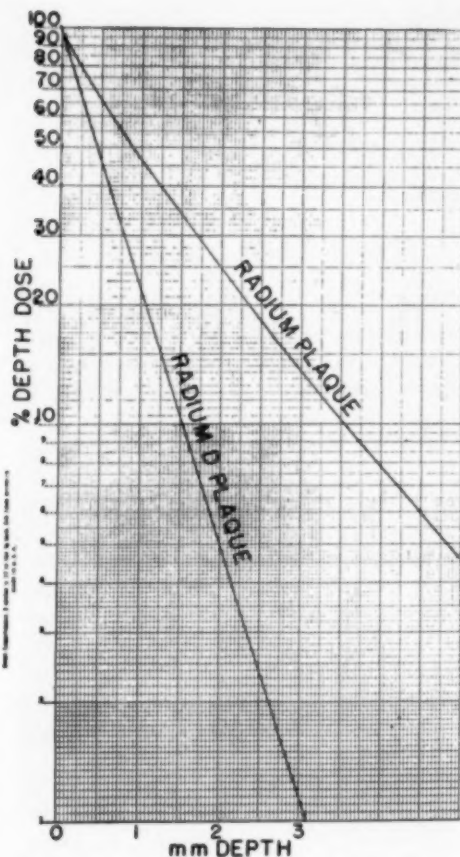


Fig. 2 (Hague). Depth dose curves of radium and radium D (D-E).

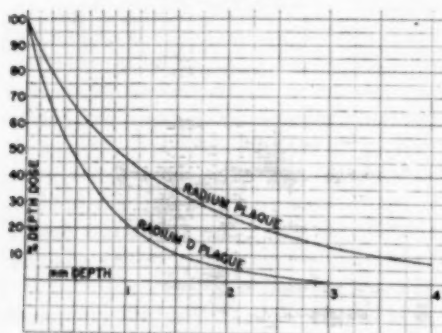


Fig. 3 (Hague). Depth dose curves from Figure 2 charted on straight coordinates to show linear relationship.

made by exposing a photographic film wrapped in a single thickness of light proof paper to the plaque as follows:

A series of graduated exposures were made with the plaque directly on the film envelope. Another series of graduated exposures were made with the film in a phantom one, two and three millimeters below the plaque. All series of exposures were made on one film so as to avoid variation in sensitivity in films and also to guard against differences incident to the processing of several films. Film densities at depth were matched in a photometer with a surface exposure and the depth intensity computed on the basis of the durations of time needed to produce equal film density on the surface and at depth.

By referring to our data, it will be evident that the amount of radiation from radium, and particularly from radium-D, falls off sharply with each millimeter of distance from the source. This is shown graphically on semilogarithmic coordinates (fig. 2) which, while they distort Cartesian comparison, show by virtue of the nearly straight line produced in each case that a main factor affecting the dose at any depth is the square of the distance, thus producing a theoretical check on our measurements.

In Figure 3, a Cartesian graph shows without logarithmic distortion the extreme difference in penetration of irradiation from radium and from radium-D.

Reading from the graph, the plaques of radium and radium-D delivered an equivalent amount of radiation at contact. At one-mm. distance, radium delivered 47 percent of the contact dose and radium-D, 21 percent. At two mm. radium delivered 24.5 percent of the contact dose and radium-D, 4.5 percent. At three mm., radium delivered 13.5 percent of the contact dose and radium-D, no quantity measurable photographically. At four mm., radium delivered 7.7 percent of the contact dose and, at five mm., it should theoretically deliver 4.5 percent.

Figure 4 shows the relative effect of radium and radium-D plaques on skin with exposure at the same distances from the skin surface. It can be seen that radium-produced visible effects at a distance of one and two mm., whereas, radium-D barely produced erythema at one mm. This biologic method is, of course, not as exact as measuring the emission from plaques at selected distances with photographic plates (table 1).

We have also calculated the depth dose curve for a contact therapy unit for an X-ray tube with a beryllium window and for Grenz rays. These values are shown in Figure 5.

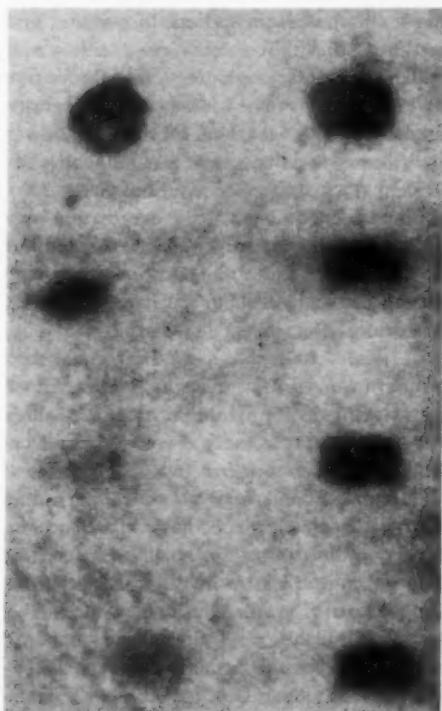


Fig. 4 (Hague). Erythema produced by radium and by radium-D plaques. (Right hand column shows erythema from oblong radium plaque at contact, 1 mm., 2 mm., 3 mm., 4 mm. The left hand column shows erythema from radium-D plaque at contact, 1 mm., 2 mm., 3 mm., 4 mm. The areas of erythema produced at 4-mm. distance are nearly cut off by the lower margin of the photo. Vesiculation was present where the photo shows mottling.)

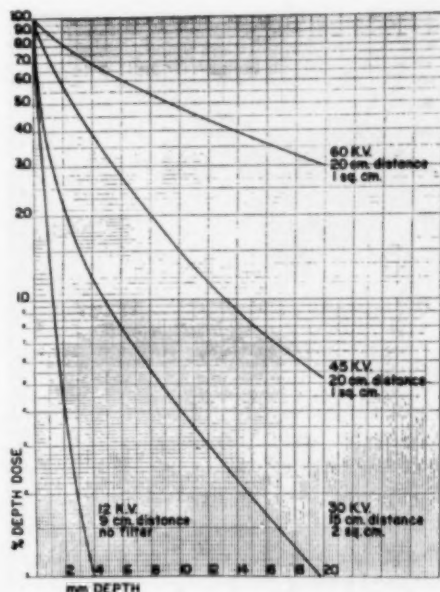


Fig. 5 (Hague). X-ray depth dose curves.

	Voltage	Filter	Distance	Area
Curve 1	60 K.V.	None	20 cm.	1 sq. cm.
Curve 2	45 K.V.	None	2 cm.	1 sq. cm.
Curve 3	30 K.V.	None	15 cm.	2 sq. cm.
Curve 4	12 K.V.	None	9 cm.	

The conventional X-ray therapy generator would seem to have slight application where it is desired to limit treatment to the anterior segment of the eye. The X-ray generators used by the dermatologist permit operation at low voltage and fairly short treatment distance. Referring to the typical dose curve for such a generator (fig. 5, curve 1) it is evident that for ophthalmologic lesions which lie at depths not exceeding four mm., the radiation dosage delivered to tissues such as the lens, deeper than the lesion, would be appreciable and only slightly less than that received by the lesion itself.

A decrease in operating voltage as well as a marked decrease in treatment distance results in the depth dose curve shown in Figure 5, curve 2. This is a typical depth dose curve for the so-called contact therapy unit when

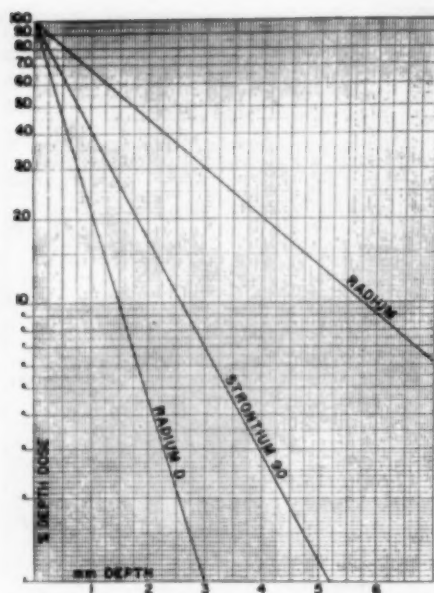


Fig. 6 (Hague). Depth dose curves with plaques in contact.

Curve 1. Conventional radium plaque
Curve 2. Radiostrontium applicator
Curve 3. Radium-D + E plaque

operated at 45 kilovolts with a treatment distance of only two cm. The depth values shown in this curve are in the right direction of lesser intensities at depth. This generator produces approximately 200 r (roentgens) per second thus making the delivery of small doses of radiation a difficult matter of correct timing. Scheie and others³ have reported on the effect of radiation from this type of generator on the normal and vascularized cornea of the rabbit.

The development of X-ray tubes with a beryllium window is a recent improvement. When this type of tube is operated at 30 kilovolts and at 15 cm. distance, the resulting depth values are as shown in Figure 5, curve 3. From this curve it is evident that the dose has been reduced to approximately 10 percent at four-mm depth. This modality would therefore seem to have potential application in the treatment of superficial eye

disease, although the accompanying curves show that it is not as safe as radium or Grenz rays.

A still further reduction in the depth dose results from the use of Grenz rays generated at 12 kilovolts. The curve shown in Figure 5, curve 4, represents the depth values when this generator is used at a treatment distance of nine cm. Here the decrease in depth dose is to one percent at four-mm. depth. As the curve shows, this modality would appear indicated for very superficial lesions.

Since the first disintegration product of radium is radon, a gas, it is possible to remove this gas from radium in solution and compress it within a small glass bulb whose walls are thin enough to permit the escape of the beta rays. The radon gas disintegrates according to the chart of Figure 1 and owes its beta-ray activity to that portion which has broken down to become radium-C.

The radon bulb can have a radiation output equivalent to as much as 0.5 gm. of radium, which makes the treatment time very short, conveniently but perhaps somewhat hazardously short.

It has a half-life period of 3.85 days which means that it is losing 16 percent of its strength every 24 hours. After a short time its beta-ray activity is reduced to a level that makes it impractical to use. A good deal of apparatus and highly trained personnel are required to collect and calibrate radon.

The radio-isotope of strontium (Sr^{90}) is also an emitter of beta rays whose energies lie between those of a radium plaque and a radium-D plaque and therefore the depth dose curve should lie between them. Curve 3, Figure 6, is that of a strontium 90 plaque as presented by Friedell and others⁴ who have written concerning the use of this plaque in eye disease.

CLINICAL OBSERVATIONS

My own interest in the use of radium in the treatment of eye diseases dates from 1942, following the publication of Dr. Alan

C. Woods's² important article on the subject and a conversation with Dr. Sanford R. Gifford. Impressed with the results which Dr. Irving Puntenney and Dr. H. E. Davis obtained with a case of tubercular interstitial keratitis which I referred to them in that year, I began to use radium in the treatment of vascularized sclerosing keratitis and then in certain other eye diseases.

I mention here my own impressions of the results to be obtained from beta irradiation only to add to the weight of evidence gathered by a number of competent and more or less enthusiastic observers.

At first I used radium rather sparingly and I do not claim experience in applying it in all of the eye diseases in which good results have been reported. Because of the somewhat complicated nature of some of these eye diseases and the tendency which they have toward more or less spontaneous remissions, I do not believe that a statistical analysis of my results would be worth while.

For some time, however, I have been fully convinced that beta irradiation of the exterior tissues of the eye is both safe and helpful. It produces marked benefit in several conditions for which I know no other effective treatment, notably in sclerosing keratitis and in the prevention of the recurrence of pterygium following excision; the tendency of a pterygium to recur, is well known. It is also my impression that beta irradiation promotes the clearing of scarred corneas, particularly where the scar is a recent development, and that it may be effectively used in conjunction with calsulphydryl for this purpose.

For the benefit of those who have not used radium extensively in the treatment of eye disease, it may be well to call attention to the fact that the beneficial effect of radiation upon the anterior segment quite clearly becomes apparent some weeks after the application.

With a plaque containing 20 mg. of radium distributed over a radiating surface of approximately 60 sq. mm., applying the plaque

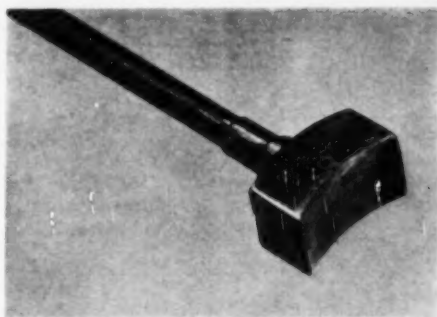


Fig. 7 (Hague). Curved radium plaque.

directly at contact with the lesion for a period of 12 minutes, using instillation anesthesia, and keeping the surface of the cornea moist, is in my hands a typical dose, which might be repeated once a week for a total of four such doses; after a rest period of four to six weeks, when benefit from the radiation may begin to be in evidence, similar divided doses may be applied for a comparable series.

Consideration of the rapid falling off of effective radiation from radium within a few millimeters from the source has led me to design a curved plaque (fig. 7) which more nearly fits the contour of the eyeball. Theoretically, the surface of the plaque might be curved in each meridian, but practically it has proved difficult enough to secure a plaque curved in one axis and, for various practical reasons, including the possibility of using this plaque over the sclera or on the skin of the lids, it has seemed best not to bring this curve to the actual corneal curvature.

With a flat plaque, such as I formerly used, applied at tangent contact with the cornea, the calculated effective dosage for various parts of the plaque at various depths in the cornea is shown in Figure 8, which also presents a similar table for the curved plaque. The much more even dosage from the curved plaque is by this comparison evident.

Since dosage time with unfiltered radium is short, a matter of minutes, it should be

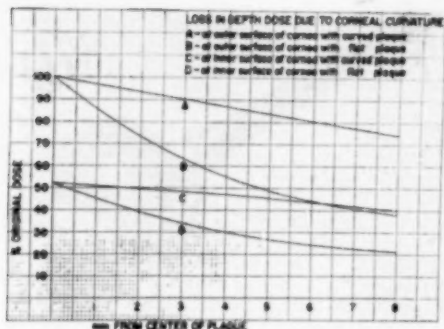


Fig. 8 (Hague). Comparison of loss in depth from ends of flat and curved applicators.

possible to apply a curved applicator directly to malignant tumors of retina and choroid, exposing the choroid as in scleral resection, without the danger to the lens associated with X rays.

It remains to be noted that, whereas the radium plaque gave a quite uniform photographic image, the radium-D plaque did not, indicating that the radioactive material in the radium-D plaque was irregularly distributed. This irregularity of distribution was rather

marked, and would seriously affect control of dosage.

CONCLUSIONS

The application of various radioactive substances to the anterior segment of the eye has been discussed, particularly from the standpoint of safe but effective therapy. Depth dose curves of radium and radium-D were calculated from photographic measurements. Depth dose curves of radioactive strontium and of various X-ray modalities were calculated.

In view of the marked differences in the depth curves of the two types of plaques, not widely apprehended, it is not surprising that considerable confusion exists among the users of these plaques. The radium-D plaque for very superficial lesions would be expected to be as effective as the radium plaque but lacks sufficient penetration for slightly deeper lesions. The fact that radium in a curved applicator appears most satisfactorily to fulfill the criteria in this limited area, for safe but effective therapy, has been commented upon.

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THE RESULTS OF BETA IRRADIATION IN OPHTHALMOLOGY*

A REPORT OF 123 CASES

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Until a short time ago radium therapy for eye conditions was usually limited to the treatment of vernal conjunctivitis and certain malignant ocular lesions. In 1939 Woods¹ reported encouraging results in the treatment of tuberculosis of the anterior ocular segment with beta irradiation.

A year later Burnam and Neill² published their experience in the same type of treatment which they applied to a number of eye conditions such as corneal scars, pterygiums, corneal vascularization, scleritis, and vernal catarrh. Burnam designed an applicator containing radon as a source of beta irradiation and this same applicator was used by Woods¹ and Iliff.³

The interest recently stimulated in this type of irradiation has been due mainly to the contributions of such workers as Ruedemann,⁴⁻⁵ Hughes and Iliff,^{3,6} and others, and to the greater development of corneal surgery.

There are three different rays in radium emanation—the alpha, beta, and gamma rays. Alpha particles have a minimal penetration and are of limited value therapeutically. The beta rays are electrons and have low penetration power, being completely absorbed by either one mm. of lead or two mm. of brass. About 60 percent of beta rays that are applied to the surface of the cornea reach a depth of one mm. Only 10 percent remain at a depth of five mm.

Gamma rays, usually employed alone in radium therapy, are radiations which are analogous to ordinary light and roentgen rays. They have a high penetrative power, even

for the most dense materials. When the limited penetration of beta rays is considered, it is evident that in the eye its usefulness is limited to treatment of the cornea and sclera.

Beta-radium therapy is useful in the treatment of vernal conjunctivitis^{2-5, 8, 11-13} and in anterior ocular tuberculosis^{1, 8} as it reduces pain and shortens the course of the disease. It is very helpful in corneal lesions where vascularization is to be inhibited or prevented, and especially in cases of lamellar keratectomy,^{7, 8} where beta irradiation prevents postoperative granulation and inhibits the overgrowth of connective tissue.

There are several types of applicators used for beta-radium therapy: the original Burnam-Neill² applicator, containing radon as a source of beta irradiation; and new applicators introduced recently are the so-called radium-D⁷⁻⁹ applicator which is a source of pure beta rays, and the Sr^{90, 10} containing strontium.

For the past two and one-half years the Department of Ophthalmology has been using beta irradiation in over 150 eyes. The treatment was carried out in conjunction with the Department of X-ray Therapy of the University Hospital.

The beta irradiation employed in the treatment considered in this report was used in the form of a radium plaque. The applicator contained 10 mg. of radium over an area of one square centimeter and had a 0.2-mm. thickness of Monel-metal filter. The dosage rate in rep (roentgen-equivalent-physical) at the surface of the applicator is not known precisely, but is more than 100 rep/minute but less than 170 rep/minute. It is believed that the approximate rate is 125 rep/minute and this is the value used in determining the data given below.

* From the Department of Ophthalmology, University of Michigan, presented at the Centennial Conference of the University of Michigan Medical School, September, 1950.

METHOD OF TREATMENT

The eye was anesthetized with 0.5-percent pontocaine and the applicator was applied in direct contact to the area to be treated. The total dose depended entirely on the condition treated and the response to the treatment. According to the recent bibliography,^{7,8} a dose of about 6,000 rep fractionated over three weeks is sufficient to obliterate corneal vessels and yet to be well tolerated by the surrounding tissues. In this study a much more conservative program was followed in an attempt to find the minimum effective dosage.

RESULTS OF TREATMENT

Various types of keratitis. Out of the 123 cases, 95 belonged to this group (table 1). Of these, 26 were patients with eczematous keratoconjunctivitis, 28 with tuberculous kerato-iritis, 13 with sclerosing keratitis, 11 with luetic interstitial keratitis, and seven with corneal scarring and vascularization.

Also included in this group was one case with traumatic keratitis, two with post-herpetic disciform keratitis, one with nummular keratitis, one with fascicular keratitis, two with Mooren's corneal ulcer, two with acne rosacea keratitis, and one with epidemic keratoconjunctivitis.

Lesions were considered healed if the eye was quiet with no corneal infiltrates and no flare or cells, and the patient was under observation for a year. Four cases out of 95 belonged to this group. In eight cases the mentioned criteria for healing were present except that the period of observation was less than a year. These eight cases were, therefore, placed in the group showing improvement.

Eyes were considered improved if there was a definite decrease of corneal infiltration and vascularization and an improvement in the subjective symptoms; 69 out of 95 belonged to this group. Eyes were classified as unimproved if, despite the treatment, there was no appreciable change at the end of the

observation; 22 patients belonged to this latter group.

In 27 cases, which had the clinical symptomatology of tuberculosis of the anterior ocular segment, the condition responded well to beta irradiation, as did the patients with eczematous keratoconjunctivitis. However, irradiation did not prevent future attacks.

The 11 cases with luetic interstitial keratitis, included in this group, responded poorly to the beta treatment, as did the cases with lupus erythematosus and acne rosacea.

The mode of action of beta irradiation in keratitis is not well known. According to the literature^{1,3,14} beta and grenz rays increase the antibody reaction in the cornea and it may be that the beneficial result is obtained in this way, or perhaps the treatment at the limbus produces occlusion of the vessels and decrease in vascularity results in improvement.

Pterygia. In cases of pterygia, where a recurrence is seen after operation, beta irradiation is especially valuable.^{2-5,8} Of 16 cases (table 2) of pterygia treated with beta irradiation, eight had been operated. In five out of the 16 the pterygium became inactive after the beta treatment while 10 showed improvement with decrease in vascularization and one did not respond.

Episcleritis. Four cases with episcleritis (table 3) were treated with beta irradiation. Of those three were recurrent in type, one was cured, and three showed improvement at the end of the observation period.

Corneal dystrophies do not respond to beta rays. Three cases of various types of corneal dystrophies showed no improvement after beta irradiation (table 4).

Vernal conjunctivitis. According to the bibliography excellent results have been obtained in vernal conjunctivitis. Recurrences are less frequent and there is an improvement of subjective symptoms. In this series only five cases of vernal conjunctivitis are included (table 5). Of these one showed improvement and four showed no appreciable change.

TABLE 1
CASES OF KERATITIS TREATED WITH BETA IRRADIATION

Number	Affected Eye	Initial Vision	Diagnosis	No. of Treatments	Interval	Total Dosage rep*	Final Vision	Results	Period of Observation
639072 (J.T.)	O.U.	2/60 3/60	Luetic interstitial keratitis	5	15 wk.	1250 O.U.	C.F. 6/60	No improvement	10 mo.
650588 (H.W.)	O.U.	H.M. H.M.	Luetic interstitial keratitis	10	6 mo.	2625 O.U.	6/30 6/16	Obliteration of vessels, inactive scarring	6 mo.
649799 (P.B.)	O.S.	— M.O.	Traumatic keratitis with scarring and vascularization	5	15 wk.	1375 O.S.	— 6/12	Marked improvement, obliteration of vessels, less scarring	6 mo.
594110 (D.E.)	O.S.	— C.F.	Postherpetic disciform keratitis	5	15 wk.	1250 O.S.	— 5/6	Healed	1 yr.
672834 (H.K.)	O.D.	6/15 —	Nummular keratitis with corneal infiltration and vascularization	5	15 wk.	1250 O.D.	6/6—4 —	Improvement	6 mo.
652016 (L.M.)	O.S.	— 1/60	Disciform keratitis	5	15 wk.	1250 O.S.	— 5/15	Improvement, obliteration of vessels less scarring	13 mo.
650383 (S.M.)	O.D.	6/30 —	Mooren's corneal ulcer	5	15 wk.	1625 O.D.	6/30 —	No improvement	2 yr.
645388 (M.J.)	O.D.	6/12 —	Fascicular keratitis	5	15 wk.	1500 O.D.	6/12 —	No improvement	6 mo.
663511 (G.S.)	O.U.	6/15 6/15	Acne rosacea—keratoconjunctivitis	5	15 wk.	1250 O.U.	6/9 6/9	Slight improvement	10 mo.
654369 (A.B.)	O.U.	3/60 5/12—2	Luetic interstitial keratitis	5	15 wk.	1250 O.U.	6/30 6/9—1	Decrease in corneal scarring & vascularization	11 mo.
627921 (G.B.)	O.U.	6/60 6/60	Luetic interstitial keratitis	5	15 wk.	1250 O.U.	6/30 6/30	Improvement in vascularization, scarring unchanged	18 mo.
609894 (J.F.)	O.U.	5/30 3/60	Luetic interstitial keratitis	3	9 wk.	750 O.U.	6/60 6/60	Minimal improvement	2 yr.
545520 (L.F.)	O.U.	C.F. C.F.	Luetic interstitial keratitis	5	15 wk.	1250 O.U.	C.F. C.F.	No improvement, did not return for further treatment	5 mo.
550649 (G.J.)	O.U.	6/30 6/30	Luetic interstitial keratitis	4	12 wk.	1000 O.U.	6/30 6/30	No improvement	6 mo.
640268 (D.L.)	O.U.	6/12 6/12	Luetic interstitial keratitis	5	15 wk.	1250 O.U.	6/9—3 6/9—3	Obliteration of vessels, no change in scarring	14 mo.
476856 (N.P.)	O.U.	6/30 6/30	Luetic interstitial keratitis	5	15 wk.	1250 O.U.	6/30 6/30	No improvement	14 mo.
578483 (W.R.)	O.S.	— 6/30	Luetic interstitial keratitis	3	15 wk.	1250 O.S.	— 6/15	Decrease in vascularization, no change in scarring	7 mo.
647857 (L.S.)	O.D.	C.F. 3 ^r	Luetic interstitial keratitis	5	15 wk.	1375 O.D.	1/60 —	No improvement	9 mo.
662760 (L.S.)	O.U.	6/15 6/30	Acne rosacea keratitis	5	15 wk.	1250 O.U.	6/9—2 6/15—1	Slight improvement, new flare-up O.D. Started, 2nd course, Beta O.D.	1 yr.
628823 (B.P.)	O.U.	6/30 6/6—2	Stage IV trachoma Trachomatous pannus	5	15 wk.	1250 O.U.	6/30 6/6	No improvement	8 mo.
662645 (O.M.)	O.D.	1/60 —	Stage IV trachoma, Trachomatous pannus	5	15 wk.	1250 O.D.	6/60 —	Slight improvement	4 mo.
490668 (I.H.)	O.D.	6/30 —	Deep corneal scarring and vascularization	5	15 wk.	1250 O.D.	6/30 —	Obliteration of vessels, scarring unchanged	9 mo.
639288 (C.U.)	O.D.	6/9—2 —	Corneal scarring and vascularization	3	9 wk.	750 O.D.	6/6 —	Complete obliteration of vessels	3 mo.
631915 (A.R.)	O.S.	— 6/60	Corneal leukoma and deep vascularization	5	15 wk.	1250 O.S.	— 6/12	Slight improvement	8 mo.
656165 (A.T.)	O.S.	— L.P.	Diffuse superficial & deep corneal infiltration & vascularization	5	15 wk.	1250 O.S.	— L.P.	No improvement	6 mo.

* Roentgen equivalent physical.

TABLE 1—continued

Number	Affected Eye	Initial Vision	Diagnosis	No. of Treatments	Interval	Total Dosage rep*	Final Vision	Results	Period of Observation
363258 (F.G.)	O.S.	6/6-3	Corneal infiltration & vascularization	6	18 wk.	1500 O.S.	6/9-1	Slight improvement	6 mo.
643772 (E.S.)	O.D.	6/30	Epidemic keratoconjunctivitis	4	12 wk.	1500 O.D.	6/15	Slight improvement	6 mo.
637797 (M.Z.)	O.D.	6/9	Interstitial keratitis	5	15 wk.	1375 O.D.	6/9	Improvement	5 mo.
559933 (M.W.)	O.D.	1/60	Eczematous keratoconjunctivitis	5	15 wk.	1250 O.D.	6/60	Improvement	14 mo.
603302 (W.W.)	O.D.	6/15	Tubercular keratitis	4	15 wk.	1250 O.D.	6/6	Marked improvement	6 mo.
641871 (G.V.)	O.U.	C.F. C.F.	Interstitial keratitis	10	8 mo.	2500 O.U.	6/60 2/60	Improvement	26 mo.
637559 (M.L.)	O.U.	6/60 6/9+3	Eczematous keratoconjunctivitis	3 2	6 wk.	750 O.D. 500 O.S.	6/9 6/9-1	Improvement in vision, less vascularization	1 mo.
290430 (H.A.)	O.S.	M.O.	Keratitis	2	3 wk.	500 O.S.	M.O.	No improvement, eye enucleated	
567254 (J.B.)	O.U.	6/30 6/30	Keratitis—secondary glaucoma	5	3 wk.	1250 O.U.	6/30 6/30	No improvement	6 mo.
613499 (B.C.)	O.S.	6/6	Eczematous keratoconjunctivitis Sclerosing keratitis	1		250 O.S.	6/6	Healed	2 mo.
630479 (B.D.)	O.D.	6/60	Tubercular interstitial keratitis	4	13 wk.	2250 O.D.	6/30	Less vascularization, corneal scarring unchanged	9 mo.
648432 (A.F.)	O.D.	6/60	Tubercular interstitial keratitis	5	15 wk.	2750 O.D.	6/6	Healed	6 mo.
650898 (N.P.)	O.U.	6/6 6/6	Sclerosing keratitis	1 4	12 wk.	2500 O.D. 1000 O.S.	6/6 6/6	Marked improvement	8 mo.
283460 (A.M.)	O.S.	3/60	Sclerosing keratitis	6	18 wk.	1500 O.S.	6/60	Slight improvement	6 mo.
649213 (W.A.)	O.S.	6/30	Eczematous keratoconjunctivitis	10	8 wk.	2500 O.S.	6/12	Healed	14 mo.
606437 (L.S.)	O.U.	6/60 6/60	Eczematous keratoconjunctivitis	5	15 wk.	1250 O.U.	6/30+ 6/30+	Slight improvement, new flare-up	1 yr.
670478 (B.F.)	O.D.	6/12	Interstitial keratitis	5	15 wk.	1250 O.D.	6/9	Improvement	8 mo.
527323 (A.M.)	O.D.	6/30	Eczematous keratoconjunctivitis	3	9 wk.	750 O.D.	6/9	Improvement	2 mo.
661268 (W.R.)	O.U.	6/60 5/60	Interstitial keratitis	5	15 wk.	1250 O.U.	6/30 6/60	Slight improvement	1 yr.
448407 (B.S.)	O.S.	4/60	Sclerosing keratitis	5	15 wk.	1250 O.S.	6/30	Slight improvement	13 mo.
633335 (M.P.)	O.U.	6/15 6/15	Deep tubercular keratitis	2	15 wk.	500 O.U.	6/30 6/6	Improvement O.S., unchanged O.D.	2 mo.
462719 (R.C.)	O.U.	6/30 6/6	Sclerosing keratitis	5 4	15 wk.	1250 O.D. 1000 O.S.	6/30 6/6	No improvement	6 mo.
642687 (K.P.)	O.D.	6/9-3	Sclerosing keratitis	2	6 wk.	500 O.D.	6/4.5-1	Marked improvement	2½ mo.
647322 (J.O.)	O.U.	6/6 6/6	Interstitial keratitis	5 6	15 wk.	1250 O.D. 1500 O.S.	6/6+4 3/4.5-2	Improvement, new flare-up O.D.	8 mo.
669464 (C.M.)	O.S.	6/15	Eczematous keratoconjunctivitis	2	6 wk.	500 O.S.	6/6-2	Improvement	1 mo.
646097 (C.R.)	O.D.	C.F.	Keratitis	3	9 wk.	2250 O.D.	6/12	Improvement in vision, less vascularization	13 mo.
673861 (R.R.)	O.D.	6/12	Eczematous keratoconjunctivitis	4	12 wk.	1000 O.D.	6/9-1	Improvement	1½ mo.
660759 (B.C.)	O.U.	6/12-1 6/9+1	Eczematous keratoconjunctivitis	4	12 wk.	1000 O.U.	4/60 4/60	No improvement	No follow-up

* Roentgen equivalent physical.

TABLE 1—continued

Number	Affected Eye	Initial Vision	Diagnosis	No. of Treatments	Interval	Total Dosage rep*	Final Vision	Results	Period of Observation
639306 (O.P.)	O.D.	6/—	Interstitial keratitis	5	15 wk.	1250 O.D.	6/9 —	Improvement	6 mo.
614989 (E.P.)	O.U.	C.F. 6/60	Eczematous keratoconjunctivitis	5	15 wk.	1250 O.U.	6/60 6/60	No improvement, new flare-up	8 mo.
644084 (J.P.)	O.U.	6/6 6/6	Mild eczematous keratoconjunctivitis	1	—	250 O.U.	6/6 6/6	Healed	19 mo.
643360 (N.T.)	O.D.	F.M. —	Tubercular interstitial keratitis	3	9 wk.	750 O.D.	6/30 —	Decrease in vascularization	No follow-up
315900 (M.H.)	O.D.	6/60 —	Eczematous keratoconjunctivitis	2	6 wk.	500 O.D.	6/6 —	Improvement	4 mo.
667342 (S.H.)	O.U.	6/12 6/30	Eczematous keratoconjunctivitis	3	2 mo.	750 O.U.	6/9 6/30	Improvement	Insufficient follow-up
646423 (L.K.)	O.U.	6/30 6/6-4	Interstitial keratitis	5	15 wk.	1250 O.U.	6/30 6/9	Decrease in corneal infiltration and vascularization	3 mo.
585205 (A.G.)	O.S.	— 6/6	Sclerosing keratitis	4	18 wk.	1125 O.S.	— 6/6	Healed	1 yr.
646796 (M.C.)	O.D.	6/6 —	Tubercular keratoiritis	3	9 wk.	1500 O.D.	6/6 —	Less vascularization, scarring unchanged	7 mo.
658078 (A.F.)	O.U.	6/30 6/30	Eczematous keratoconjunctivitis	4	12 wk.	2000 O.U.	6/30 6/30	No change on day of discharge	No follow-up
651450 (A.M.)	O.D.	6/12 —	Eczematous keratoconjunctivitis	4	12 wk.	1000 O.D.	6/9 —	Improvement, no active vascularization, scarring unchanged	8 mo.
625215 (J.O.)	O.U.	6/6 6/12	Eczematous keratoconjunctivitis	10 5	6 wk.	2500 O.D. 1250 O.S.	6/6 6/12	Improvement	26 mo.
639569 (E.P.)	O.U.	6/9 6/30	Eczematous keratoconjunctivitis	3	9 wk.	1500 O.U.	6/6 6/30	Decrease in vascularization day of discharge	No follow-up
672070 (C.S.)	O.U.	6/9-2 6/9-4	Eczematous keratoconjunctivitis	3	9 wk.	1500 O.U.	6/12-2 6/9-3	Decrease in vascularization, improved	8 mo.
650108 (W.S.)	O.U.	3/60 6/60	Eczematous keratoconjunctivitis	3	9 wk.	1750 O.D. 1500 O.S.	6/15 3/60	Decrease in vascularization	No follow-up
455376 (N.T.)	O.S.	— 6/90	Eczematous keratoconjunctivitis	5	15 wk.	2750 O.S.	— 6/60	No improvement	5 mo.
635793 (L.M.)	O.U.	Chart 6/30	Tubercular interstitial keratitis	5	15 wk.	3750 O.U.	6/60 6/30	Decrease in vascularization, no flare-up	14 mo.
641812 (L.K.)	O.S.	— 6/30	Keratoiritis	5	15 wk.	1500 O.S.	— 6/6	Healed	1 yr.
647322 (A.K.)	O.U.	6/6 6/6	Tubercular interstitial keratitis	5 6	15 wk.	1250 O.D. 1500 O.S.	6/6-4 6/4.5-2	New flare-up O.D., improvement O.S.	6 mo.
669464 (J.Mc.)	O.S.	— 6/15	Eczematous keratoconjunctivitis	2	6 wk.	500 O.S.	— 6/6-2	Improvement	1 mo.
637797 (A.M.)	O.D.	6/9 —	Tubercular interstitial keratitis	5	15 wk.	1375 O.D.	6/9 —	Improvement	5 mo.
559933 (A.C.)	O.D.	1/60 —	Eczematous keratoconjunctivitis	5	15 wk.	1250 O.D.	6/60 —	Improvement	14 mo.
603302 (A.H.)	O.D.	6/15 —	Tubercular interstitial keratitis	4	12 wk.	1250 O.D.	6/6 —	Healed	7 mo.
641871 (O.B.)	O.U.	C.F. C.F.	Tubercular interstitial keratitis	10	8 wk.	2500 O.U.	6/60 2/60	Decrease in vascularization, scarring unchanged	26 mo.
592496 (M.B.)	O.D.	C.F. —	Tubercular interstitial keratitis, episcleritis	3	9 wk.	750 O.D.	6/60 —	Improvement in symptoms & vascularization	2 mo.
133901 (R.B.)	O.S.	— C.F. poorly	Sclerosing keratitis	5	15 wk.	1250 O.S.	— C.F.	No improvement	15 mo.
666489 (J.B.)	O.S.	— C.F.	Interstitial keratitis	5	15 wk.	1250 O.S.	— 5/60	Decrease in vascularization, improvement of symptoms	6 mo.

* Roentgen equivalent physical.

TABLE 1—continued

Number	Affected Eye	Initial Vision	Diagnosis	No. of Treatments	Interval	Total Dosage rep*	Final Vision	Results	Period of Observation
658077 (W.H.)	O.S.	— 1/60	Sclerosing keratitis	5	15 wk.	1250 O.S.	— 1/60	No improvement	2 mo.
660606 (T.C.)	O.U.	6/30 6/15	Eczematous keratoconjunctivitis	10	8 mo.	2500 O.U.	6/30 6/30	No improvement	8 mo.
650898 (A.F.)	O.U.	6/6 6/6	Sclerosing keratitis	1 4	12 wk.	250 O.D. 1000 O.S.	6/6 6/6	Healed	8 mo.
283460 (A.G.)	O.S.	— 3/60	Sclerosing keratitis	6	8 wk.	1500 O.S.	— 5/60	Decrease in vascularization, scarring unchanged	6 mo.
649213 (E.G.)	O.S.	— 6/30	Eczematous keratoconjunctivitis	10	8 wk.	2500 O.S.	— 6/12	Improvement	14 mo.
606437 (H.H.)	O.U.	6/60 6/60	Eczematous keratoconjunctivitis	5	15 wk.	1250 O.U.	6/30+ 6/30+	Decrease in vascularization, new flare-up	1 yr.
670878 (J.H.)	O.D.	6/12 —	Interstitial keratitis (tubercular)	5	15 wk.	1250 O.D.	6/9 —	Improvement	8 mo.
527323 (S.H.)	O.D.	6/30 —	Eczematous keratoconjunctivitis	3	9 wk.	750 O.D.	6/9 —	Improvement	2 mo.
661268 (M.H.)	O.U.	6/60 5/60	Tubercular interstitial keratitis	5	15 wk.	1250 O.U.	6/30 6/60	Decrease in vascularization, scarring unchanged	6 mo.
448407 (M.H.)	O.S.	— 4/60	Deep sclerosing keratitis	5	15 wk.	1250 O.S.	— 6/30	Unchanged	13 mo.
633335 (L.K.)	O.U.	6/15 6/15	Deep tubercular keratitis	2	6 wk.	500 O.U.	6/30 6/6	Unchanged O.D., improvement O.S.	2 mo.
462719 (F.K.)	O.U.	6/30 6/6	Recurrent episcleritis, sclerosing keratitis	5 4	15 wk.	1250 O.D. 1000 O.S.	6/30 6/6	No improvement	6 mo.
642687	O.D.	6/9—3 —	Sclerosing keratitis	2	6 wk.	500 O.D.	6/4.5—1	Improvement	2½ mo.
579848 (O.L.)	O.S.	6/9	Eczematous keratoconjunctivitis	3	15 wk.	1250 O.S.	6/6	Healed	6 mo.
662768 (E.S.)	O.D.	6/12	Tubercular kerato-iritis	6	15 wk.	1500 O.D.	6/9+	Healed	7 mo.

* Roentgen equivalent physical.

TABLE 2

CASES OF PTERYGIUM TREATED WITH BETA IRRADIATION

Number	Eye Affected	Operation	No. of Treatments	Interval (weeks)	Total Dosage rep*	Results	Period of Observation (months)
658935 (J.B.)	O.D.	No	3	9	750		Insufficient follow-up
659365 (L.B.)	O.S.	Yes	5	15	1250	Good	10
651362 (B.C.)	O.D.	No	5	15	1300	Excellent	9
667136 (R.M.)	O.S.	Yes	1		250	Good	1½
649576 (G.E.)	O.S.	Yes	1		250	Good	3
324009 (C.M.)	O.D. recur	No	2	6	750	Improvement	1
662668 (E.B.)	O.D.	Yes	5	15	1250	Improvement	1
658936 (M.P.)	O.D. recur	Yes	4	12	1000	Good	6
302683 (C.S.)	O.D.	No	3	9	1125	Improvement	3
476856 (E.S.)	O.D.	No	5	15	1875	Excellent	6
652007 (E.G.)	O.D.	Yes	2	6	750	Improvement	2
449134 (A.H.)	O.S.	No	2	6	750	Improvement	Insufficient follow-up
639764 (C.H.)	O.U.	Yes	3	9	875 O.U.	Excellent	3
640405 (L.H.)	O.D. recur	Yes	5	15	1500	Excellent	6
638760 (W.K.)	O.U.	No	5	15	1875 O.U.	Excellent	6
663481 (C.R.)	O.D.	No	2	6	500	Improvement	Insufficient follow-up

* Roentgen equivalent physical.

TABLE 3
CASES OF EPISCLERITIS TREATED WITH BETA IRRADIATION

Number	Eye Affected	No. of Treatments	Interval (weeks)	Total Dosage rep*	Results	Period of Observation
153157 (P.C.)	O.S.	2	6	500	Improvement	2 mo.
585205 (H.J.)	O.S. recur	4	12	1000	Cured	1 yr.
462719 (F.K.)	O.U. recur	5 O.D. 4 O.S.	15	1250 1000	Improvement	6 mo.
647084 (R.K.)	O.D. recur	5	15	1250	Improvement	Insufficient follow-up

* Roentgen equivalent physical.

TABLE 4
CASES OF CORNEAL DYSTROPHIES TREATED WITH BETA IRRADIATION

Number	Type and Eye Affected	No. of Treatments	Interval (months)	Total Dosage rep*	Results	Period of Observation (months)
665362 (E.B.)	Endothelial corneal dystrophy	3	1½	750 O.U.	No change	2
432874 (R.R.)	Fuchs's endothelial dystrophy and bullous keratitis, O.S.	5	3	1250	No change	7
670329 (M.S.)	Endothelial and epithelial corneal dystrophy, O.D.	5	3	1250	No change	5

* Roentgen equivalent physical.

TABLE 5
CASES OF VERNAL CATARRH TREATED WITH BETA IRRADIATION

Number	Degree	Area of Involvement	No. of Treatments	Interval (months)	Total Dosage rep*	Results	Period of Observation
638775 (J.C.)	Severe	Upper lids & limbus	5 O.U.	3	1250	Improvement	1 yr.
662322 (B.P.)	Severe	Upper lids & limbus	10 O.U.	10	2500	No improvement	27 mo.
629486 (R.G.)	Severe	Upper lids & limbus	10 O.U.	14	2500	No improvement	28 mo.
552154 (D.H.)	Severe	Upper lids	5 O.U.	3	1250	No improvement	11 mo.
660456 (G.N.)	Severe	Upper lids & limbus	10 O.U.	10	2500	No improvement	20 mo.

* Roentgen equivalent physical.

TABLE 6
SUMMARY OF 123 CASES TREATED WITH BETA IRRADIATION

Diagnosis	No. of Cases	Healed	Improved	No Improvement
Various types of keratitis	95	4 (4.21%)	69 (72.6%)	22 (23.2%)
Pterygium	16	5 (31.2%)	10 (62.5%)	1 (6.25%)
Vernal conjunctivitis	5	0 (0%)	1 (20%)	4 (80%)
Episcleritis	4	1 (25%)	3 (75%)	0 (0%)
Corneal dystrophies	3	0 (0%)	0 (0%)	3 (100%)
Total	123	10 (8.13%)	83 (67.5%)	30 (24.4%)

A survey is now under way using larger total dosage over a shorter period of time employing Sr⁹⁰ strontium applicator.

CONCLUSIONS

1. Ninety-five cases with various types of keratitis were treated with beta irradiation. Of these four, or 4.21 percent were healed, 69, or 72.6 percent, showed improvement, and 22, or 23.2 percent, were unimproved. A comparison of vision before and after treatment indicated that in 56 cases, or 59 percent, the vision improved to two or more lines, in 36, or 37.9 percent, was maintained, and decreased in three, or 3.16 percent.

2. Beta irradiation proved to be of great value in treatment of vascularized and recur-

rent pterygia and in episcleritis; five cases of severe and long standing vernal conjunctivitis were relatively insensitive to irradiation.

3. Corneal dystrophies and lupus erythematosus are not benefited by beta rays.

4. The amount of irradiation is dependent upon the duration of the condition. In this series superficial corneal lesions with newly formed blood vessels were more radiosensitive and responded well to lower doses. Deep and long-standing vascularized corneal lesions responded poorly to small doses and required more intensive radiation.

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APPLICATORS FOR BETA IRRADIATION OF THE EYE*

A REVIEW AND COMPARISON

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Beta irradiation of the eye is a well-established form of therapy which is both safe and effective when used properly in the conditions for which it is indicated. Investigators have reported separately on several different radiation applicators, but, regardless of the excellence of the articles dealing with these devices individually, many points of comparison with other applicators have not been emphasized. It is the purpose of this paper to review and consolidate the descriptions of four separate sources of radioactivity and eight different beta-radiation applicators used in ophthalmology and to compare them and their clinical attributes with each other.

RADIUM

Radium, as used in applicators, is a solid in the form of a sulfate, bromide, or chloride. Radioactivity accompanying the decay of radium consists of alpha and beta particles and gamma rays. The first decay product is radon, followed by a series of transmutations from radium A to G.

The disintegration stops with radium G, or lead, which is stable; but the previously formed decay products have their own radiation characteristics, the sum of which constitutes the total radiations from radium.

In the transmutation of radium to radon, only a small amount of low-energy gamma rays and some alpha particles are emitted. Therefore, of the total radiations from radium, the beta and gamma emanations which are clinically significant come from disintegration products and not directly from the radium itself.

Alpha particles (helium nuclei) produced

by radium decay may be disregarded clinically, since they are completely absorbed within the applicator before reaching tissue. Total absorption of alpha particles occurs with as little as a sheet of paper or with 0.1 mm. of unit-density material.

Primary electrons (beta radiation) possess energies which vary from zero to a maximum, the average of which has clinical significance (penetrating power) when beta particles from different sources are compared.

The most energetic beta particles of this series are derived from radium C, and less energetic ones are derived from radium B and some from radium E. Older radium samples contain more radium E and therefore have a slightly greater specific beta activity.

The clinically important beta particles from radium decay have the following energies:

	Maximum Energy	Average Energy
Radium B	0.65 Mev.*	0.23 Mev.
Radium C	3.15 Mev.	0.65 Mev.

* Mev. = million electron volts.

For these beta particles the half-value layer (HVL), the depth at which the surface dose is reduced by one half, in tissue or other unit-density material, is variously rated at about one mm. or slightly more. The depth-dose at four mm., the level of the lens, is approximately 15 percent of the dose delivered at the surface.¹ The maximum distance reached in tissue by a few long-range electrons is 15 mm.²

The above properties of radium are also possessed by radon, the equilibrium radiations from which are identical with those from radium. The physical characteristics of the beta particles from radioactive strontium (Sr^{90}) are strikingly similar; those from

* From the Department of Ophthalmology, Indiana University School of Medicine.

radium D+E compare less favorably.

It is only because of its relatively small proportion of highly penetrating gamma radiation (HVL, 10 mm. lead), that radium can be used at all in beta applicators for the eye, since it is not possible to eliminate selectively these highly penetrating rays. The ratio² of beta to gamma is approximately 25, in terms of electrostatic units of ionization, from a radium plaque of presumed optimum load—that is, "full strength" or 5 mg./cm².

The surface dose-rate of such an applicator is of the order of 5,000 beta roentgens per hour. These values of beta/gamma ratio and dose-rate are variable with the geometry of each applicator.

Although moderately expensive, radium is readily available to individual physicians and institutions alike; it may be obtained on a rental basis, or purchased outright, in which case its cost may be amortized over long periods. The half-life of radium is 1,590 years, far greater than any other radioactive source considered in this study.

ILIFF APPLICATOR*

Description. This is a 50-mg. radium plaque designed by Iliff³ for ophthalmic use. It is rectangularly prismatic in shape, measuring 6 by 6 by 12 mm., overall, and made of silver with a Monel-metal face. The sides are one-mm. thick, the backing, three-mm., and the Monel metal at the active face, 0.1 mm. in thickness.

A 28-cm. handle is provided but, because of the repeated and prolonged exposures necessary with this applicator, it is desirable to have a holding device, like the one described by Iliff, or the holder devised by Stevenson⁴ for the radium-D applicator and easily adapted to this one, or the plastic contact lens with a window the size and shape of the applicator, as described by Haik.⁵ The Stevenson holder is more difficult to

place, but it and the Haik lens have the advantage of being movable with the patient's head.

Advantages. The half-life of radium is so long that the output of the Iliff applicator can be considered constant and permanent. In this one respect it is better than applicators using any other radioactive source, particularly better than those utilizing radon with a half-life so short that the radioactive load must be replaced every week or two.

The Iliff applicator is readily available, like radium-D; whereas, radon is available only at great expense and inconvenience. That the Iliff applicator can be obtained on a rental basis as desired is an advantage, and there is no required approval from the Atomic Energy Commission, as has been necessary in the case of the Sr⁹⁰ applicator and other radioactive isotopes.

The Iliff applicator produces energetic beta particles which are well suited to many of the indications for beta irradiation of the eye. This quality of beta radiation from radium is the same as that from radon, similar to that from Sr⁹⁰, and superior to that from radium D.

Disadvantages. Self-absorption of beta particles within the Iliff applicator reduces its effectiveness, and results in longer clinical treatments. These longer treatments are disadvantageous, per se, and, in addition, produce inaccuracies in dosage calculation because of the difficulty of accomplishing steady fixation of the eye and applicator for the required time.

Gamma radiation, moreover, being of highly penetrating nature, is not affected by self-absorption within the applicator, and is delivered from the entire 50-mg. load. The resulting, lowered, beta/gamma ratio means increased gamma-ray exposure to both patient and operator.

Radium must be kept away from personnel and photo-sensitive supplies, and is stored in a thick lead well which is usually heavy enough to cause some inconvenience.

* Manufactured by the Radium Chemical Co., Inc., New York, New York.

The cost of the Iliff applicator is a fraction more than the radium-D applicator (about \$1,000), and considerably more than the Sr⁹⁰ applicator (\$300).

Clinical considerations. Iliff⁶ recognized clinically the loss of efficiency from self-absorption within the applicator and stated that a 10-minute contact exposure (30 gram-seconds) with this radium plaque produced about the same effect as a 4.5 or 5 gram-second dose with radon.

Considering this, and on the basis of previous studies⁷ using unfiltered radon in the Hughes applicator as the standard, which produced minimal lesions on rabbit corneas with 10 gram-second doses, the calculated, minimal inflammatory dose with the Iliff applicator should be about 60 or 70 gram-seconds.

This calculation, based on clinical observations is in fairly close agreement with the recent experimental findings⁸ that single, contact doses of 75 gram-seconds, with a 50-mg. Iliff applicator (No. 124383), were required to produce minimal, inflammatory lesions on the rabbit corneas.

Compared, therefore, with the Hughes applicator containing radon, the Iliff applicator is less efficient, the beta effectiveness of its 50-mg. load being reduced to the equivalent of about 6.5 mg. and causing over seven times as much gamma exposure for beta-radiation treatments of equal effect.

Clinical treatments are usually eight to 10 minutes each with this applicator and, during this time, there is exposure of all of the ocular structures; but the greatest gamma radiation hazard is to the lens, which receives not less than 75 gamma r during such treatment. The dose required to produce the same clinical effect with radon causes a lens exposure to gamma radiation of only about 10 r per treatment.

The penetrating, gamma, or X-ray radiations from the nearly pure beta emitters, Sr⁹⁰ and Ra-D, are of very low intensity and can be disregarded clinically. (Lens tolerance

is variously estimated at from 300 to 1,000 gamma r.)

The whole-body, gamma radiation to the operator for a typical 10-minute treatment with the Iliff applicator, depends on several variables, but the gamma exposure was found⁹ to be less than five mr., as recorded on Kelley-Koett pen-style dosimeters worn at applicator level, when the operator used one minute for handling and placing the applicator and the remaining nine minutes observing the patient at a distance of eight feet from the applicator. (Whole-body gamma tolerance is considered to be 300 mr./wk.).

The exposure of the operator's hands is also a variable quantity, depending on the care and facility used in handling, but local tissue tolerances are not exceeded if a holding device is used and if the applicator is handled only with instruments and with reasonable care.

If there is any doubt, as in beta clinics of large volume, monitoring devices should be used to determine the local and general exposures of the operators.

The Iliff applicator is suitable for use in certain cases of benign and malignant, small, superficial neoplasms of the eye and adnexa, corneal vascularization when not extensive, pterygia, and the less severe cases of vernal conjunctivitis. Extensive lesions should be irradiated only with proper caution, because of the increased gamma exposure to the patient resulting from repeated applications with the Iliff instrument.

GENERAL-PURPOSE PLAQUES

Description. Radium applicators designed for general radiologic use have had some application in ophthalmology. Having active faces usually made of 0.1 mm. Monel metal, these plaques are, as a rule, 1.0 to 1.25 cm. in diameter when full strength, but lesser strength applicators may be somewhat larger. They are said to be "full-strength" when they contain radium in the amount of 5.0 mg./sq. cm. A typical applicator of this type

usually produces about 5,000 r/hour (roentgens beta) and has a beta/gamma ratio of the order of 25.²

Advantages. These applicators carry a small load of radium and are therefore relatively inexpensive; moreover, they are commonly found among ordinary radiotherapy facilities. The self-absorption of beta particles is less in these applicators; and, consequently, their beta/gamma ratio is somewhat higher and more favorable than that of the radium applicator of Iliff.

Disadvantages. Because of their shape and size, the general-purpose radium plaques used in radiologic and dermatologic conditions are not easily applied to the eye. Full-strength applicators can be used, but half-strength applicators are unsatisfactory. Treatment times are so long (reportedly up to one hour,⁹ although this seems unusually long), that fractionation of dosages becomes necessary, resulting in more and frequent treatments and more inaccuracies in dosage calculation for given areas. The presence of gamma radiation, as in all radium and radon applicators, is a disadvantage in storage and handling and must be taken into account in treatment schedules.

Clinical considerations. These applicators have a much more nearly optimum load as regards the beta/gamma ratio. Gamma-ray hazard, therefore, while not eliminated, is somewhat less for both patient and operator than with the Iliff applicator.

Smith⁹ reported on the use of a full-strength applicator every six weeks for three treatments in 40 cases of Mooren's ulcer. About half of these did well for long periods, on which basis he presumed a permanent cure; 25 percent were apparently cured but had been treated too recently to classify as permanently cured; the others responded poorly or not at all.

Because of the awkwardness of ocular application, and the long treatment-time necessary for applicators of this type, they have had only limited acceptance for use in eye conditions. Fractionation of dosage is

probably the best method of using these general-purpose plaques because of the long treatment times involved. Fractionation, per se, although useful in general radiation practice, has not been fully evaluated in terms of beta irradiation of the eye.

Further clinical considerations are much the same as those for the Iliff applicator.

LEDERMAN APPLICATOR*

A radium plaque shaped like a spatula and adjusted to the eye by means of a slotted brass holder has been designed by Lederman.¹⁰ He reported using single doses of 1,500 r, and the treatment time was about 11 minutes, which indicates a radium load of approximately 5.0 mg./sq. cm. This applicator is, therefore, essentially a "full-strength" radium plaque which has been adapted in size and shape to ophthalmic use, thereby overcoming one major disadvantage of ordinary plaques.

Lederman,¹¹ for nearly 10 years, has also used a radium plaque of 5.0 mg. contained in a brass box 8.0 mm. sq., with 0.1-mm. Monel face, with a stated calibration of 8,300 r per hour. It is used with a lid-speculum holder for application by quadrants to the cornea.

Other advantages, disadvantages, and clinical considerations are the same for these applicators as already described for all general-purpose plaques.

RADON

This radioactive gas is the first product of radium disintegration, and, exactly like radium, depends on its daughter substances, particularly radium B and radium C, for its clinically important radiations; therefore, the radiation characteristics of radium and radon (which has reached equilibrium with its decay products) are identical. These have already been described.

* Made by Messrs. Johnson, Matthey and Co., London.

The beta radiation from radon and radium differs quantitatively, however, because radium is a solid; whereas, radon, being a gas, has practically no beta loss through self-absorption. Radon, therefore, has a high beta/gamma ratio, approximately 27. It also possesses a high specific activity, making it possible to obtain great radiation intensity from a relatively small applicator (1,000 mc., for example, occupies only 0.664 cu. mm., under standard conditions).

Beta-ray dose-rate values determined for radium at zero filtration apply more nearly to radon applicators than to those containing radium, because of the self-absorption within radium applicators. Since calibration values are seldom available for radon ophthalmic applicators, it is desirable at times to use such data for estimating the dose rate of these applicators.

The specific, beta-ray dose-rate² at zero filtration for radium (B + C) is 1,180 r/mg. hr., 520 r/mg. hr. for radium-E, and 1,710 r/mg. hr. for radium in final equilibrium.

The collection of radon gas is a complicated process requiring a large supply of radium as well as special equipment and technical personnel. Such facilities are infrequently found. Radon is commercially available; but, because of the relatively larger amounts used in ophthalmic applicators, it is expensive to use; and, moreover, its short half-life (3.83 days) multiplies this expense and causes considerable inconvenience.

BURNAM APPLICATOR¹²

Description. This applicator, first designed and used in 1927, contains radon gas collected in a glass bulb, five mm. in diameter, which is placed in a brass capsule having two-mm. side walls and a round, four-mm. portal at its distal end. All of this, in turn, fits into a similar but slightly larger capsule attached to a handle 35 cm. in length.

The amount of radon in this applicator varies commonly from 200 to 500 mc. but occasionally¹³ may contain as much as 800 mc.

The distance between the active, glass bulb and the surface being treated is one mm. There is no filtration except that afforded by one mm. of air and by the wall of the glass sphere. This is enough filtration to absorb all alpha particles but allows a maximum beta/gamma ratio.

Advantages. The Burnam applicator eclipses all others in potency and in short treatment time. Its beta particles are of energetic quality, like those of Sr⁹⁰ and radium, but without the self-absorption found in radium, radium-D, and Sr⁹⁰ applicators. It has, like the Hughes applicator (q.v.), the advantage of a high beta/gamma ratio.

Disadvantages. For the Burnam applicator, the disadvantages are chiefly those associated with the expense and inconvenience of frequently obtaining large amounts of radon. Bulk radon sells commercially at about \$1.50 per mc., which usually means large quantities are used only by institutions having their own emanation plants.

There is, of course, undesirable gamma radiation from the Burnam applicator, but the high beta/gamma ratio makes possible a maximum beta effect with minimum gamma radiation. As with any applicator using radon, gamma radiation (about 10 r, gamma, per average application) is actually much less per treatment than with radium applicators; nevertheless, any amount of gamma radiation of this order is a disadvantage, and it must constantly be considered in the calculation of dosages.

The hazard to the operator is also a disadvantage of the Burnam applicator, since the intensity of the load is so great that considerable care is necessary in handling, transport, and storage.

Clinical considerations. With the great intensity of the Burnam applicator, treatment time (usually calculated in gram-seconds) is reduced to a matter of a few seconds, the exact time depending on the amount of radon in the applicator. Because of the short half-life of radon (3.83 days), dose calculations must be corrected hourly for loss of

potency. Tables are available to simplify the calculation of this loss, which is roughly 16.5 percent per day.

Since the beta/gamma ratio is high, the eye under treatment receives relatively small amounts of gamma rays from dosages ordinarily employed. The operator, however, receives increased gamma exposure during the manipulations and handling of this potent applicator.

Based on data for radium, it is estimated that the accepted tolerance of 300 mr./wk. for whole-body radiation would be approached by the operator giving about 12 applications, when a total handling time of 30 seconds per treatment is allowed for an applicator of 500 mc. In any case approximating anything like this amount of exposure, however, individual monitoring should be employed, and no reliance should be placed in such estimates, because of the large number of variable factors involved.

Although limited by expense, difficulty of procurement, and gamma-ray hazard to the operator, the Burnam applicator with its short treatment times, energetic beta radiation, and high beta/gamma ratio is a most useful instrument, when available, and when used properly, for beta irradiation of the eye.

HUGHES APPLICATOR¹⁴

Description. Mounted on the end of a small, metal-rod handle, which is about 18 inches in length, this applicator is kidney-shaped to fit the curvature of the limbus, has sides of silver, and is open at the treatment face.

This kidney-shaped, open face, with slightly concave edges to fit the curvature of the globe, is about 60 sq. mm. in area (5 by 12 mm.) and contains small, glass, radon tubes, usually three in number, arranged parallel and about one-mm. apart and held in place by a thin layer of household cement (Duco®) on the backing plate.

These radon needles are usually about five mm. in length and slightly less than one mm.

in diameter, so that the radioactive area enclosed by them averages about 4 by 5 mm. With each loading the radon-tissue distance is slightly variable but is usually near contact without actually touching, probably most often about one mm. This arrangement is intended to achieve as much uniformity of radiation as possible.

Advantages. The advantages of this applicator are chiefly those of radon, perhaps the best source of beta radiation for use in ophthalmology, although artificial sources, like the betatron and some of the artificially radioactive isotopes, must await further animal and clinical experimentation before a proper evaluation of them can be made. The radon of the Hughes applicator assures an energetic beta spectrum, a high beta/gamma ratio, and adequate intensity.

The use of small glass tubes makes the collection of radon technically easier, and because smaller amounts are used, for example, 50 mc., the radon load is more economical than in the Burnam applicator.

The shape and design of the Hughes applicator make its application to the globe, especially the limbus, easy and accurate.

Studies have not been made comparing the Burnam and Hughes applicators, but, since they both use radon and have approximately the same filtration factors and radon-tissue distances, very little difference in clinical effectiveness would be expected on an equal gram-second basis.

Compared with others, however, the Hughes applicator is more efficient: on an equal gram-second basis, it is two and one-half times as effective as the radium-D applicator,⁷ six to eight times the Iliff radium applicator,^{7,8} and preliminary results indicate that it is probably nearly four times as efficient as the Sr⁹⁰ applicator.⁸

Disadvantages. Commercial laboratories charge something less than \$100 for a Hughes-applicator load of about 50 mc. When the half-life of radon (3.83 days) is also considered, this economic disadvantage is compounded.

Where the facilities of an emanation plant are available, the use of the Hughes applicator is only mildly inconvenient and much more practical. Long-distance transportation of this applicator creates an added difficulty because of the time consumed and the consequent loss of potency.

Besides the minor storage problems which add to the inconvenience of this applicator, the presence of gamma rays causes a radiation hazard; this is more important to the operator than to the patient, however, since in ordinary dosages gamma-ray exposure of the recipient eye is not troublesome or dangerous.

Both local and whole-body radiation tolerances of the operator must be respected in handling radon. These disadvantages attributable to gamma rays are also found in the Iliff and other radium applicators, but not in applicators using Ra-D or Sr⁹⁰.

The minor variations in geometry which occur with each loading of the Hughes applicator constitute a disadvantage which has not been of serious consequence, since good clinical reproducibility is possible when the loading is done carefully.

Clinical considerations. Although treatment times are longer than with the Burnam applicator, the Hughes applicator is, nevertheless, easy to use clinically, and much more so than the radium, Ra-D, or Sr⁹⁰ applicators.

Treatment time is short enough that ocular fixation is not a serious problem (as it often is with solid element plaques) and it has been used effectively in the treatment of all the common indications for beta irradiation of the eye.

Except for its expense and inconvenience of procurement to most operators, the Hughes radon applicator is one of the best and most practical for use in ophthalmology.

ACTIVE-DEPOSIT APPLICATORS

When some metals are held in an atmosphere of radon gas for about two hours, they become coated with a thin layer of solid ma-

terial which is radioactive. This layer, known as "active deposit," is composed of radon disintegration products (radium A, B, and C) which produce alpha, beta, and gamma emanations. The production of active deposit is technically difficult and is possible only with a large source of radium and an emanation plant.

Quick¹¹ described active-deposit applicators made of lead foil cut into shapes and used for the treatment of vernal conjunctivitis. This is the only type of ophthalmic applicator which allows alpha particles to reach the tissues.

It is interesting that Quick had used, but with dissatisfaction, radon in a glass bulb similar to the applicator Burnam had devised three years previously, and also had made applicators of wood and metal to which glass radon tubes were fastened with paraffin; actually, these were prototypes of the applicator which Hughes has successfully developed more recently.

Quick, however, dismissed this arrangement as technically unsatisfactory; and declared that the active deposit on lead foil was his choice as the best means of application. Since then, reportedly, little has been done to develop the use of this active-deposit form of ophthalmic beta irradiation.

RADIUM D

This naturally radioactive isotope of lead is one of the daughter substances of radium. It has a half-life of 22 years, and disintegrates by a weak beta emission to radium E, which then is responsible for the clinically effective beta particle (average energy, 0.34 Mev.; maximum, 1.17 Mev.). The product of radium-E decay is radium F which transforms to lead by alpha emission. The disintegration of radium D is accompanied by no gamma radiation of clinical importance.¹²

The decay scheme of radium D is characterized by only one beta emission (that from radium E) of therapeutic significance; whereas, radium and radon are character-

ized by two beta particles, one each from radium B and C.

RADIUM-D APPLICATOR*

*Description.*¹⁷ This circular plaque has an outside diameter of nine mm. and an active diameter of 5.6 mm. (25 sq. mm. active area) at the contact face. The radioactive source is approximately 10 mc. of radium-D in the standard applicator; on special order, applicators containing 20 mc. are available, although self-absorption reduces the additional effective output by about 50 percent (increasing the load by only about 5.0 mc. instead of 10 mc.).¹⁸

The radium D is covered at the contact face with 0.05 mm. of aluminum foil, and the surface dose rate is said to be of the order of 200 beta roentgens-equivalent per minute (3.66/sec.). The applicator is equipped with a short handle or may be used with a holding device⁴ which clamps to a lid speculum.

Advantages. The advantages of this applicator are derived chiefly from the fact that radium-D, like Sr^{90} , is an almost pure beta emitter. The small amounts of secondary X rays (*Bremsstrahlung*) from this applicator are of no clinical significance; therefore, handling and storage are relatively simple and nonhazardous.

Also, there is no danger of significant photon exposure of the lens or deeper ocular structures, a hazard which must be carefully controlled from radon and radium applicators, particularly the latter.

Availability of the radium-D applicator is good; and, although the cost (about \$1,000) and the half-life (22 years) are favorable, particularly when compared with radon, nevertheless the strontium applicator is cheaper, although more awkward to apply; and the Iliff applicator, which costs about the same, has a much longer half-life than radium-D.

* Manufactured by Canadian Radium and Uranium Corporation, New York, New York.

Disadvantages. An important disadvantage of this applicator is its low output. Compared with radon on an equal gram-second basis in clinical and animal experiments,⁷ the radium-D applicator was found to be only about two-fifths as effective as radon. This results in prolonged treatment time for the patient, requiring ocular fixation in some cases for as long as 15 to 20 minutes.

Moreover, the low energy of the beta particles from the radium-D applicator reduces the depth dose and clinical effectiveness (although the filtration from self-absorption within the applicator may improve this somewhat). In the cornea, for example, even the more energetic beta particles from radium and radon are inadequate for many deeply vascularizing processes.

Clinical considerations. Because of the low energy of its beta particles and its low output, the radium-D applicator is used best for the most superficial and less extensive clinical conditions, such as corneal vascularization confined to small areas in the anterior stroma or thin pterygia of small or medium size.

For other clinical indications such as deeper corneal vascularization or more extensive lesions, other sources of beta irradiation furnish the methods of choice.

Attempts to increase the depth dose by lengthening the exposure time with the radium-D applicator may dangerously increase the caustic effects at the surface. There is practically no whole-body radiation to the operator with this applicator.

RADIOACTIVE STRONTIUM (Sr^{90})

This fission product is the only one of the artificially radioactive isotopes which has been used in an ophthalmic applicator for clinical use. There are others which could be used, like Ru^{106} ; and P^{32} has been used as a source of beta radiation in animal experiments,¹⁹ but Sr^{90} seems to have the most nearly ideal combination of desirable characteristics: 20-year half-life (19.9 ± 0.3 years),²⁰ beta emission without significant gamma radiation, beta particles of adequate

energy, adequate specific activity, availability, and low cost.

The decay scheme²⁰ of Sr^{90} is characterized by two beta spectra, a weaker one (maximum energy, 0.65 Mev.; average,²¹ 0.195 Mev.) from Sr^{90} which results in the formation of yttrium-90, and a more energetic one (maximum, 2.16 Mev.; average,²¹ 0.8 Mev.) which transforms Y^{90} into the stable end-product of this series, zirconium-90.

The depth-dose²⁰ at four mm. (lens level) is indicated to be about six percent of the surface dose, and it is less than one percent at a tissue depth of 6.5 mm.

The half-value layer of the beta radiation from Sr^{90} applicators is of the order of one mm. of tissue (Friedell, et al.,²¹ 0.9 mm.; and Tracerlab,²⁰ 1.0 mm.). This is approximately the same as that for beta rays from radon or radium.

Although the energy of beta particles from radium reaches a greater maximum, the figures just quoted indicate that the particles from Sr^{90} attain a slightly higher average energy. This is probably because the proportion of longer-range electrons is higher in Sr^{90} and Y^{90} than it is in radium C. Also, in radium, but not in Sr^{90} , a number of atoms disintegrate with the release of some of their energy in the form of gamma radiation.

STRONTIUM-90 APPLICATORS

Friedell and his associates²¹ were the first to use Sr^{90} in an ophthalmic applicator. Following the lead of this laboratory model, commercial physicists have recently developed a clinical model, the "RA-1 medical applicator."^{*}

Description. This Tracerlab applicator (RA-1) has the following specifications:²⁰ the radioactive material, about 25 mc. of Sr^{90} in equilibrium, is spread uniformly at the applicator face which has an active diameter of 7.8 mm. (47.7 sq. mm. area) and an actual diameter of 12.7 mm.

^{*} Manufactured by Tracerlab, Inc., Boston, Massachusetts.

The Sr^{90} is covered by two mils of stainless steel and 10 mils of aluminum and hermetically sealed. This totals 0.3 mm. and is slightly more filtration than in the radium-D applicator (0.05 mm. Al.) and in the Iliff radium applicator (0.1 mm. Monel).

Since the photon activity of Sr^{90} is very low, only a clear plastic disc, 10 cm. in diameter and 6.0 mm. in thickness, is used as a shield for the hand; this disc is held in position on the applicator handle.

Whereas, Friedell's model contained about 100 mc., was said to have a surface dose rate of 5.4 beta roentgens per second, and was used for clinical doses of from 60 to 100 seconds each, the commercial applicator contains only about 25 mc. of Sr^{90} and, although somewhat variable with different applicators, the surface dose rate of one such applicator (RA-1, no. 29) was calibrated by the manufacturer at 22.9 r (rep) per second (compare this with the stated radium-D dose rate of 3.66 per second, or full strength radium plaque dose rates of usually less than two per second), and yet preliminary results with this applicator indicate that it requires a much longer, not shorter, clinical dose than that of the Friedell model.

Current investigations¹ with this Tracerlab applicator (RA-1, no. 29) have revealed a minimal inflammatory dose of 35,000 r (rep) on the rabbit cornea, consistent with which are the prolonged treatment times found necessary to produce a clinical response in human eyes, 12,000 to 14,000 r.

For this particular applicator, it is apparent that the effective surface dose-rate has been found to be much less than that expected from its millicurie load of 25 mc. The applicator, therefore, on the basis of these preliminary findings, has a radon-equivalent of about 7.0 mc., approximately the same as that of the Iliff plaque with which it has been compared in these same studies.

Advantages. The principal advantages of the applicator are derived from the fact that Sr^{90} is a pure beta emitter without clinically significant photon activity, greatly reducing

TABLE 1
SUMMARY—COMPARISON OF SIX BETA-IRRADIATION APPLICATORS FOR OPHTHALMIC USE

Beta Applicator	Iliff Radium Applicator	General-Purpose Radium Plaques	Burnam Radon Applicator	Hughes Radon Applicator	Radium-D Applicator	SR-20 Applicator ("R.A.-Y")
Amount of radioactive source of material (actual load)	50 mg. (approx.)	Full-strength = 5 mg./sq. cm.	Frequently about 100 mc. (varies)	Frequently about 60 mc. (varies)	10 mc. (standard) to 20 mc.	35 mc. (approx.)
Clinical potency (effective load)	About 7 mg.	Unknown (varies)	300 mc. (or same as load)	60 mc. (or same as load)	About 4 mg.	About 7 mc.
Availability of applicator	Good	Good	Poor	Fair	Good	Good
Approximate cost	\$1,000	\$25 per mg.	\$450 (400 mc.)	\$100 (60 mc.)	\$1,000 (10 mc.)	\$400
Half-life	1,590 yr.	1,590 yr.	3.83 days	3.83 days	22 yr.	20 yr.
Dose-rate calibration (beta)	Undetermined	About 1.5 r/sec. for a full-strength applicator (varies)	Undetermined (calculated)	Undetermined (calculated)	3.3 r per sec. for the 10 mc. applicator	22 r per sec. (varies)
Approx. treatment time for applicator with load indicated	8-10 min.	15-30+ min.	13 sec.	67 sec.	10-20 min.	Undetermined (about 10 min.)
Adaptability of design (size and shape)	Fair	Usually poor (varies)	Good	Good	Good	Poor
Adaptability for use with mechanical holding device	Fair	Poor	(Not required)	(Not required)	Good	Poor
Average beta energy (Mev. = million electron volts)	Ra-B 0.23 Mev. Ra-C 0.65 Mev.	Ra-B 0.23 Mev. Ra-C 0.65 Mev.	Ra-B 0.23 Mev. Ra-C 0.65 Mev.	Ra-B 0.23 Mev. Ra-C 0.65 Mev.	Ra-D (too low) Ra-E 0.34 Mev.	Sr ⁹⁰ 0.195 Mev. Y ⁹⁰ 0.90 Mev.
Percent beta depth-dose at lens level (4 mm.)	Unknown; similar to gen-purpose plaques, probably >15%	About 15% ¹	Unknown; similar to gen-purpose plaques, probably <15%	Unknown; similar to gen-purpose plaques, probably <15%	Undetermined (less than 5%)	6% ²⁰
Minimum inflammatory dose for rabbit cornea (M.I.D.)	75 gram-seconds	Undetermined	Undetermined (probably similar to Hughes)	10 gram-seconds	25 gram-seconds	35,000 r (38 gram-sec.)
Possible gamma-ray hazard to lens	Considerable	Considerable	Slight	Slight	None	None
Gamma-ray exposure at 1 cm. distance during one average clinical average	75 r	Unknown (varies)	10 r	10 r	Negligible	Negligible
Possible gamma-ray hazard to operator	Considerable	Considerable	Considerable	Some	None	None

both the inconvenience of handling and the potential hazards of use. Sr^{90} has a 20-year half-life, an advantage over radon, but much inferior to radium. Pure beta emission and a half-life measured in years are advantages of the radium-D plaque also, but the Ra-D applicator has less energetic beta particles and less millicurie load than the Sr^{90} applicator.

Compared with radium, Sr^{90} theoretically has a larger proportion of high energy electrons than Ra-C, although the HVL ratings of the two are approximately the same, about one mm. of unit-density material.

Availability and economy are favorable attributes of the Sr^{90} applicator, which can be purchased at about one third of the cost of the radium-D and Iliff (50 mg. radium) applicators, and, of course, at a much smaller fraction of the cost of repeatedly using commercial radon.

Disadvantages. The disadvantages of the Sr^{90} applicator, on a purely physical and economic basis, at first would appear to be few. The Sr^{90} applicator, however, has not been fully evaluated experimentally and clinically, but it may not come up to earlier expectations.

If the just-mentioned preliminary results are substantiated by further studies now in progress, and if these findings are not greatly different with other similar strontium applicators, it will mean, as in the case of the radium-D applicator,⁷ seriously prolonged treatment times in the clinic. Radon is probably something over three times as effective as the Sr^{90} applicator being used in these studies, when the two applicators are compared on an equal gram-second basis.

Since, with our present Sr^{90} applicator (RA-1, no. 29), some of the treatment times exceed 10 minutes, the lack of a mechanical holding device for this instrument is a disadvantage, at times causing considerable inconvenience.

The applicator is too large in diameter to be applied without some difficulty when treat-

ing the upper or lower limbus or other limited areas.

Although there has been an increased tendency to ulceration after Sr^{90} irradiation of the rabbit corneas used in current studies, the clinical translation of this finding remains to be evaluated. Its threat, nevertheless, must be considered a disadvantage until further experience has proved otherwise.

Clinical considerations. If treatment times prove to be as prolonged for all Sr^{90} applicators as for the one used in our clinic, it will be inconvenient to use for many ocular conditions, especially those which are extensive enough to require multiple applications. Accuracy of dosage, moreover, is difficult to obtain when ocular fixation and steadiness of the applicator must be maintained during long periods.

In general, the effects of clinical treatments are certain to be unpredictable with these applicators at first, because of the fact that the physical measurement of beta radiation and calibration of beta applicators is not yet fully dependable as a basis for calculating the dosage which will produce an expected radiobiologic effect. Therefore, it is necessary for clinicians using a new applicator to proceed with great caution, at least for several months, until effective but safe doses can be established, or, ideally, first to standardize each new applicator on the rabbit cornea before attempting any clinical use.

It would appear, preliminarily, that the Tracerlab Sr^{90} applicator (RA-1), as it is now constructed, may have only limited use in ophthalmic conditions usually amenable to beta-radiation therapy, although the exact indications and limitations will have to be determined by further experimentation and clinical experience, in addition, perhaps, to modification of the present applicator design and dose rate.

CONCLUSION

Several ophthalmic beta-irradiation applicators are reviewed and compared. The choice of a beta applicator for clinical use

must be made according to the user's needs. Since these needs vary, the problem must be individualized, and there can be no logical generalization concerning a single, "best" applicator. Regarding this problem, how-

ever, many of the characteristics which might be considered important are used as points of comparison for the applicators discussed.

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PRACTICAL SUGGESTIONS FOR THE PREPARATION AND MAINTENANCE OF STERILE OPHTHALMIC SOLUTIONS*

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Following recent communications^{1,2} on the subject, numerous inquiries were received requesting practical suggestions for the preparation of sterile ophthalmic solutions that would be relatively resistant to contamination after opening. This paper will present simple methods for making such solutions, methods that should be readily applicable to ordinary retail and hospital pharmacy procedure.

Although these communications emphasized the dangers inherent in contaminated commercial eye solutions, there was no intent to minimize the hazards inherent

in similar contamination of eye solutions prepared in pharmacies. The main source of danger as regards commercially prepared solutions is the long time interval between manufacture and use by the patient, which permits contaminants to grow profusely. Hospital pharmacies and, often, retail pharmacies are accustomed to prepare large stock bottles of commonly prescribed ophthalmic solutions which, if made without regard to sterility and without preservatives, often serve as excellent culture media. In either case, by the time the patient uses the solution it may be loaded with organisms.

The bacterium that, for practical purposes, may be considered the major, or even the

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sole offender of importance, in the light of recent experiences, is *Pseudomonas aeruginosa* (*B. pyocyaneus*), which can cause the most serious type of corneal ulcer encountered. It grows readily in most media, producing pigments that have antibacterial actions. This is probably the reason pure cultures are grown from drugs infected with *Pseudomonas*.

Solutions of the following ophthalmic drugs have been found to be contaminated with this organism: (1) Fluorescein, (2) eserine, (3) pilocarpine, (4) scopolamine, (5) atropine, (6) ethyl-morphine hydrochloride, (7) cocaine, (8) nupercaine, (9) pontocaine, (10) cortisone, (11) sulfonamides, (12) methyl cellulose, (13) sodium chloride, and (14) tap water.

Since our own experience has covered contaminations with almost all of the drugs listed, some of which (methyl cellulose, saline solution, and tap water) are reported here for the first time, we believe that there are very few ophthalmic drugs, including antibiotics, in which the organism cannot grow.

An excellent paper on the subject was written by McCulloch in 1943.³ He stressed the special tendency of the *Pseudomonas* to grow in both fluorescein and eserine and recommended the addition of merthiolate or chlorobutanol as the best anti-infective agents. McCulloch stated that five of his series of 18 cases of corneal ulcers due to *Ps. aeruginosa* were traced to contaminated eye solutions.

In the clinical experience of one of us (F. H. T.), it appears that almost every *Pseudomonas* infection encountered was due to contamination of eye solutions or, possibly, ointments. In fact, it is amazing how few clinical infections actually do occur in view of the many times we have found abundant growth of the bacteria in such eye solutions, indicating how effectively the *intact* corneal epithelium serves as a barrier against micro-organisms.

A bacterial study of the fluorescein in use

throughout a hospital, undertaken by one of us some years ago, showed that all 26 bottles were infected with *Ps. aeruginosa*; 10 out of 15 solutions in the offices of ophthalmologists were likewise contaminated. Since nosedrops have also been found to contain *Pseudomonas*,⁴ a warning concerning their use in ophthalmic solutions should be given.

SUGGESTED PROCEDURE

We have found that the technique herein advocated is successful and will result in bacteria-free solutions. Infection with viruses during compounding is extremely unlikely, although theoretically possible. Contamination of eye solutions by viruses appears to occur as a result of inoculation of the solution by the eye-dropper after accidental contact with an infected eye.

EQUIPMENT

The equipment necessary is quite inexpensive, easily obtainable from laboratory supply houses, and occupies very little space. Hospital pharmacies and other pharmacies using stock bottles of solutions need:

1. An ordinary pressure cooker adjustable to 15-lb. pressure to sterilize bottles and droppers. (In a hospital these may be autoclaved.)

- 2.* A Selas porcelain candle (0.02 porosity, catalog number V.F.A.-88) supplied with mantle and rubber stopper to fit a 1,000-cc. filter flask. Many types of ceramic or asbestos filters carry electrical charges which may remove active ingredients from solutions. The Selas type is neutral.

3. A 1,000-cc. filter flask.

4. A water-powered vacuum pump with pressure tubing.

5. A Westinghouse ultraviolet "Sterilamp" (S.U.-793).

For the preparation of individual non-stock prescriptions, a smaller Selas candle (0.02 porosity, catalog number V.P.-86, 1.0

* These are manufactured by the Selas Corporation of America, Philadelphia, Pennsylvania.

inch by 7.25 inches)* and a 125-cc. filter flask with a one-hole rubber stopper to fit are needed.

METHOD

The procedure is as follows:

1. All equipment in contact with the solutions must be sterilized. The individual bottles and droppers are sterilized in the pressure cooker at 15-lb. pressure for 30 minutes. They are assembled loosely, not airtight, to avoid collapse of the rubber nipples. After cooling, the caps may be tightened.

2. The prescription is compounded in the usual fashion, using a saturated solution of chlorobutanol as the vehicle. To save time, it is advisable to prepare such a vehicle in advance because of the low solubility of the preservative. The solution is then filtered through the Selas filter into the flask, and later poured into the sterile container.

3. All filtration and transfer of solutions must be done directly under exposure of the Sterilamp to avoid airborne contamination. The lamp is placed immediately above the field of operation so that the pharmacist's eyes and face are not exposed to the ultraviolet rays. Other sterile techniques such as a face mask or sterile gloves are not required except when many individual small units of the drug are to be prepared at one time.

In hospital pharmacies it is preferable to fill a number of individual small dropper bottles immediately, rather than to use large stock bottles. Cork stoppers should *never* be used because they are difficult to sterilize and, due to their spongy texture, may carry infection. Separate droppers obviously are unsatisfactory.

This filtration procedure is practical for almost all ophthalmic solutions in common use except fluorescein and methyl cellulose, which clog ceramic filters.

Since autoclaving or boiling will not alter the staining properties of fluorescein it may be sterilized by these methods. Merthiolate (1:10,000) should be used as a preservative. Chlorobutanol, which is destroyed by pro-

longed heating, may be added to warm solutions as an extra precaution.

Methyl cellulose may similarly be heat-sterilized, with merthiolate, and brought back to its original clarity by refrigeration at 5°C. for 24 hours.

Heat sterilization of ophthalmic solutions, either by boiling or autoclaving, is widely used, especially in hospitals. With the exception of fluorescein, boric acid, sodium propionate, metycaine, and holocaine, as a general rule all ophthalmic medicaments, especially alkaloids, are altered in potency and in chemical character by heat sterilization. These changes accelerate the deterioration of the active drug.

If only heat sterilization is available to the ophthalmologist, he should remember that solutions so sterilized may show variations in potency and activity, as well as untoward reactions due to degradation of the active drug. Merthiolate (1:10,000) should be used as a bacteriostatic agent. Such solutions are best replaced after seven days. In general, it is felt that drugs sterilized by heat should be used only in operating rooms and should be discarded the same day.

What precautions should the ophthalmologist take in regard to solutions used in his office? He should, first of all, insist on obtaining sterilely prepared solutions, with added preservatives, made in accordance with the principles already outlined. These sterile solutions should be bottled in small containers (7.5 to 15 cc.), never in large stock bottles. If he does not care to discard a rarely-used bottle of an expensive solution, he may add a few crystals of chlorobutanol with a sterile forceps every few weeks. In addition, the ophthalmologist and his assistant must guard against contamination of the eyedropper, especially if it has touched an infected eye. If bacterial contamination is suspected, the dropper may be re-sterilized by boiling or by alcohol. If viral infection is suspected, the dropper or the solution should be discarded.

The choice of effective anti-infective

agents to maintain sterility is of the greatest importance. Recently in Britain, three *Pseudomonas* corneal ulcers occurred in one hospital.⁵ They were traced to contaminated bottles of eserine and saline which had originally been prepared sterily, but had been in use for a short time.

There are several reasons why chlorobutanol and merthiolate are advocated as preservatives. First, they are compatible with all commonly used ophthalmic drugs. Second, they appear more effective against *Pseudomonas aeruginosa* (*B. pyocyaneus*) than other antiseptic agents recommended. Third, they are not inactivated by body fluids. Of the two, chlorobutanol is preferable, because sensitivities to it have not been encountered in our experience and must be extremely rare.

Quaternary ammonium compounds are not compatible with fluorescein, or salicylate and nitrate radicals. They may be inactivated by soaps. Moreover, their use against *Pseudo-*

monas is not recommended.⁶ Furthermore, in high concentrations they may prove irritating. In addition, there is evidence that these compounds may also be inactivated by some types of rubber because of the curing agents used.

Since the publication of the communications^{1, 2} which pointed out the lack of specific governmental regulations concerning the sterility of eye medicaments and stressed the hazards of secondary ocular infections that may occur in the contamination of commercially-prepared eye solutions, several investigations have been made and it is hoped that the proper legal safeguards will be enacted to prevent such infections in the future. One definite advance has been made: the American Medical Association Council on Pharmacy and Chemistry now requires sterility of ophthalmic solutions as a prerequisite for council approval.

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EFFECT OF ACTH ON NORMAL OCULAR TENSION*

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The purpose of this study was to determine the effect of ACTH on the intraocular pressure of normal eyes. The sodium-retaining effect of this hormone has suggested that it might cause some elevation of intraocular pressure.

Data on patients with known glaucoma have been reported by Blake, Fasanella, and Wong¹ who observed that ACTH does not

reduce intraocular pressure in primary glaucoma. In several patients with uveitis receiving ACTH, McLean² observed that an exacerbation of secondary glaucoma might occur and, in fact, that secondary glaucoma might develop when it was not present prior to treatment. In the recent Gifford Memorial Lecture, Woods³ noted the inconsistent results of ACTH and cortisone in secondary glaucoma, in some cases the tension being dramatically controlled and in others the tension being unaffected.

* From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital.

TABLE 1

RECORD OF INTRAOCULAR PRESSURE MEASURED BEFORE AND DURING ACTH THERAPY
(When initial dose differs from that being given on the day of reexamination, both dosages are listed.)

Patient	Age, Sex and Race	Diagnosis	Therapy	Eosino- phil Response	Re-exami- nation (Day of Treat- ment)	Tension Before Rx (mm. Hg Schiotz)	Tension While on Rx (mm. Hg Schiotz)
#1 M. G.	19 WF	Disseminated lupus erythematosus	20 mg. q6h I.M.	Yes	5th	19 19	18 17
#2 M. F.	44 WF	Bronchial asthma	Start 50 mg. q6h I.M. Day of exam 10 mg. q6h I.M.	Yes	7th	15 15	15 15
#3 L. B.	44 WF	Rheumatoid arthritis	25 mg. q6h I.M.	Yes	4th	20 20	23 23
#4 J. S.	35 WM	Marie Strumpell arthritis	25 mg. q6h I.M.	Yes	6th	19 17	19 19
#5 H. M.	45 WF	Rheumatoid arthritis	25 mg. q6h I.M.	Yes	6th	15 15	19 19
#6 H. W.	19 WM	Disseminated lupus erythematosus	25 mg. q6h I.M.	Yes	16th	19 19	16 16
#7 K. K.	44 WM	Rheumatoid arthritis	15 mg. q6h I.M.	Yes	9th, 13th	23 22	27 21 26 23
#8 J. F.	36 WM	Ulcerative colitis	25 mg. q6h I.M.	Yes	5th	20 19	22 19
#9 F. H.	29 WF	Disseminated lupus erythematosus	Start 25 mg. q6h I.M. Day of exam 5 mg. q6h I.M.	Yes	9th	17 15	17 19
#10 J. B.	55 WM	Rheumatoid arthritis	15 mg. q6h I.M.	Yes	9th	17 15	17 17
#11 S. S.	41 WM	Disseminated lupus erythematosus	20 mg. q6h I.M.	Yes	16th	14 13	17 17
#12 G. P.	45 WF	Rheumatoid arthritis	20 mg. q6h I.M.	Yes	10th	19 19	16 16
#13 C. J.	36 CF	Sarcoidosis	50 mg. I.V. q.d.	Yes	7th	19 19	17 19
#14 B. S.	28 CF	Sarcoidosis	50 mg. I.V. q.d.	Yes	3rd	19 21	19 19
#15 A. H.	20 CM	Sarcoidosis	50 mg. I.V. q.d.	Yes	9th	19 19	19 16

METHOD OF STUDY

Twenty-one patients on the medical wards of The Johns Hopkins Hospital were used as subjects. Their ages ranged from 18 to 66 years. Only two of these had intraocular

disease: one had sarcoid lesions involving the iris but no active inflammation of the eye and the other had diabetic retinopathy.

The initial dose of ACTH varied from 15 to 35 mg., every six hours, intramuscularly.

TABLE 2

PROVOCATIVE TEST FOR GLAUCOMA: INTRAOCULAR PRESSURE BEFORE AND 30 MINUTES
AFTER INGESTION OF 1,000 CC. OF WATER

(When initial dose of ACTH differs from that being given on day of test, both dosages are listed.)

Patient	Age, Sex and Race	Diagnosis	Therapy	Eosinophil Response	Day of Treat- ment on which Test Per- formed	Control Tension (mm. Hg Schiøtz)	Water Test Tension at 30 Min. (mm. Hg Schiøtz)
#1 T. W.	22 WM	Diabetic retinopathy	35 mg. q6h I.M.	Yes	5th	23 23	26 25
#2 A. G.	37 WF	Disseminated lupus erythematosus	25 mg. q6h I.M.	Yes	23rd	17 20	20 21
#3 M. G.	19 WF	Disseminated lupus erythematosus	50 mg. I.V. q.d.	Yes	8th	24 23	28 25
#4 C. J.	36 CF	Sarcoidosis	50 mg. I.V. q.d.	Yes	7th	17 19	19 19
#5 B. S.	28 CF	Sarcoidosis	50 mg. I.V. q.d.	Yes	14th	19 19	23 23
#6 M. B.	24 WF	Myasthenia gravis	30 mg. q6h I.M.	Yes	11th	20 20	17 17
#7 G. P.	45 WF	Rheumatoid arthritis	Start 25 mg. q6h I.M. Day of test 20 mg. q6h I.M.	Yes	10th	16 16	21 21
#8 L. D.	36 WM	Rheumatoid arthritis	50 mg. I.V. q.d.	Not determined (excellent clinical response)	5th	27 27	30 30
#9 W. W.	18 CM	Acute rheumatic fever	20 mg. I.V. q.d.	No (excellent clinical response)	19th	22 22	24 24
#10 S. C.	66 CF	Multiple myeloma	25 mg. q6h I.M.	No (un- satisfactory clinical response)	12th	15 17	20 20

In six patients 20 to 50 mg. were administered intravenously each day. The patients were placed on a four-gm. salt diet with potassium chloride supplement. They were carefully followed. Frequent eosinophil counts and daily weight and blood-pressure determinations were taken.

The first 15 patients were handled as follows:

Prior to onset of treatment, an examination was performed which included vision,

manifest refraction, external, slitlamp, and ophthalmoscopic examinations. The intraocular pressure was measured using a standard Schiøtz tonometer. At intervals varying from the third to the 16th day after onset of therapy, and while the patient was still under active treatment, an identical examination was performed.

Examinations were performed at various times of day, from early morning to evening; in one case, an all-day tension curve

was taken while the patient was on treatment. In every case but one, the hormone produced a satisfactory eosinophil response or clinical response or both.

Results are shown in Table 1. There was no significant change in tension in this group of patients while on ACTH. A borderline elevation in Patient 7 was not present when measured four days later. The single patient on whom an all-day tension curve was performed showed no elevation. There was no effect on visual acuity or refractive error.

In a second group of 10 patients, including four of those already studied, a provocative test for glaucoma was performed while under active ACTH therapy. The water test was used, according to the method outlined by Sugar.⁴ One liter of water was administered. Tension was measured before administration, 30 minutes later, and, in some instances, at 60 minutes. An elevation of 9 mm. Hg or over 32 mm. Hg was considered a positive test. In one case cold-pressor and venous-congestion tests were performed.

Results are shown in Table 2. In no case was there an abnormal rise in tension fol-

lowing the water test. In one case the cold-pressor and venous-congestion tests were likewise negative.

It should be noted that all patients in this series were on a moderately salt-restricted diet. Even on such restriction there was slight fluid retention in some patients as determined by weight gain. The results of this study do not entirely rule out the possibility of an effect on intraocular pressure when there is no salt restriction. However, on the standard ACTH regime, which includes salt restriction, no effect was noted.

SUMMARY

1. In a group of 15 patients with normal or nonglaucomatous eyes, no significant elevation in intraocular pressure was detected while on ACTH treatment.

2. In the same group, no change in visual acuity or refractive error was noted while on treatment.

3. In a group of 10 patients under active ACTH treatment, the response to provocative tests for glaucoma was negative.

The Johns Hopkins Hospital (5).

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OPHTHALMIC MINIATURE

I find that the whole operation takes from two to three minutes—
twenty to thirty cataracts in an hour.

Lt. Col. Henry (Jullunder) Smith,
British Medical Journal, September 26, 1903.

CORTISONE IN OCULAR DISEASE: FURTHER STUDIES*

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In a preliminary report¹ the results of the treatment of 142 eyes with cortisone at the Wills Hospital were analyzed. This paper is an account of the follow-up of those cases, plus a similar study of 202 additional eyes which were also treated with cortisone. The study was continued primarily to increase the number and length of observations, and particularly to determine the influence of this hormone on traumatic and postoperative wound healing, on sympathetic ophthalmia, phaco-anaphylactic and hypertensive uveitis.

The methods of cortisone therapy used in this series of cases are outlined in Table 1. The eye was anesthetized with three drops of tetracaine hydrochloride (0.5 percent) before the subconjunctival injections. Cortisone eye drops were suspended in normal saline or 1:5,000 zephiran solution.

Most of the eyes in this series were treated at the onset with subconjunctival cortisone. Cortisone eye drops, in the dilutions described, were used principally in those cases which had improved with subconjunctival injections, but which had tended to relapse if cortisone therapy was not continued. Corti-

sone was used systemically in those cases which had not responded adequately to subconjunctival therapy.

The administration of systemic cortisone, in the manner noted in Table 1, was continued no longer than 12 days in each case. If no significant improvement had occurred in that time, the eye was considered not to be improved by cortisone when used systemically. Cortisone used over an indefinite time cannot be evaluated readily as a therapeutic agent, as many ocular inflammations are self-limiting.

CONCURRENT THERAPY

In most of the cases, when indicated, mydriatics or miotics and hot compresses were used along with the cortisone. Many of the cases had had fever therapy and/or antibiotics with no improvement before cortisone was begun. Subsequent improvement was obtained with fever therapy in two cases of posterior uveitis which had not improved with systemic cortisone therapy.

CRITERIA OF EVALUATION

Those cases which revealed changes from active, severe inflammation to little or no inflammation were considered to be *improved*. This improvement had to progress to com-

*From the Research and Clinical Departments of the Wills Hospital. Presented at the third Wills Eye Hospital Clinical Conference, March, 1951.

TABLE 1
METHODS OF CORTISONE THERAPY EMPLOYED IN PRESENT STUDY

Subconjunctival cortisone	{ 1/20 cc. (1.25 mg.) daily × 3 1/10 cc. (2.50 mg.) daily × 3
Cortisone used as eyedrops	{ Cortisone diluted 1 to 4 in normal saline. Cortisone diluted 1 to 4 in 1:5000 zephiran solution.
Cortisone used systemically	{ Cortisone 100 mg. every 8 hours for 3 doses, Then— Cortisone 100 mg. every 12 hours for 2 doses, Then— Cortisone 100 mg. daily for the duration of the course of treatment.
Retrobulbar cortisone	{ Cortisone 2 cc. (50 mg.) plus ½ cc. Novocain 2%

TABLE 2
 OCULAR CONDITIONS TREATED WITH CORTISONE

Diagnosis	Etiology	Mode of Therapy		Number of Eyes	Im- proved	Unim- proved	Re- lapsed
		Subcon- junctival	Drops				
Blepharitis	Staphylococcus? Seborrhea? Allergy?		5	5	3		2
Blepharoconjunctivitis	Atropine	5	5	5	4	1	
Ocular pemphigus	?	2	2	2		2	
Erythema multiforme	Allergy?	2	2	2		2	
Vernal conjunctivitis	Allergy?		6	6	3	3	
Episcleritis	Allergy?	2	3	5	3	1	1

plete quieting of the disease process or the case was considered to have *relapsed*. Most of the cases which relapsed were subsequently improved with further cortisone therapy. *Unimproved* was the descriptive term used for all those cases which did not respond significantly to cortisone therapy. The results in 22 cases did not lend themselves to such evaluation. These cases are reported but not tabulated.

TYPES OF CASES AND RESULTS

The types of cases studied, the number of eyes treated, the method of therapy, and the results of therapy are listed in Tables 2, 3, 4, and 5 and further summarized in Tables 7, 8, and 9. The results obtained in the treatment of palpebral, conjunctival, corneal, scleral, and uveal diseases with cortisone were almost identical with those reported

earlier¹ and are similar to the results reported by others.^{2-10, 19-23} The results obtained in a few conditions merit special attention.

POSTOPERATIVE UVEITIS

Of the 26 cases of postoperative uveitis which were not thought to be either sympathetic ophthalmia or phaco-anaphylactia, only four were not improved. The results in these cases were most gratifying since many of the cases had not responded to other forms of therapy, including antibiotics and fever therapy, which had been given previous to cortisone.

PHACO-ANAPHYLACTIC UVEITIS

Four cases of phaco-anaphylaxis were treated with cortisone locally, only one of which failed to respond to therapy.

 TABLE 3
 OCULAR CONDITIONS TREATED WITH CORTISONE

Diagnosis	Etiology	Mode of Therapy			Number of Eyes	Im- proved	Unim- proved	Re- lapsed
		Subcon- junctival	Drops	Sys- temic				
Marginal corneal ulcers	Allergy?	4	1		5	3	2	
Deep corneal ulcers	?	10	5		11	6	5	
Ring abscess of the cornea	?	1			1		1	
Phlyctenular keratitis	Allergy	1			1		1	
Dendritic keratitis	Herpes simplex	5			5	2	2	1
Superficial keratitis	Virus: Allergy?	6	6		9	8		1
Sclerosing keratitis	Allergy	3	2		3	2	1	
Chemical keratitis	Lime	4	2	1	6	5	1	
Interstitial keratitis	Congenital lues	8		1	9	1	8	
Interstitial keratitis	Nonluecic	10	3	1	11	5	2	5
Corneal dystrophy	?	1	2		3		3	

TABLE 4
OCULAR CONDITIONS TREATED WITH CORTISONE

Diagnosis	Etiology	Mode of Therapy				Number of Eyes	Improved	Unimproved	Relapsed
		Subconjunctival	Drops	Systemic	Retrobulbar				
Anterior uveitis	Undiagnosed	88	22	5		99	64	20	15
	Postoperative	21	15			26	20	4	2
	Traumatic	14	13			18	11	7	
	Sarcoid	3				3		3	
	Herpes zoster	3	3	3		5	2	1	2
Diffuse uveitis	Phaco-anaphylaxis	3	2			4	3	1	
	Sympathetic ophthalmia	7	6	9		16	5	5	6
	Vogt-Koyanagi	2		2		2		2	
	Harada	2		2		2		2	
	Posterior uveitis—Undiagnosed	16	2	14	8	35	16	18	1
Endophthalmitis—Postoperative		1	1	1		1		1	

POSTERIOR UVEITIS

Thirty-five cases of nonspecific uveitis were treated in this series. Eighteen cases were not improved; many of these cases may have been treated inadequately, that is, with subconjunctival or drop cortisone. Of the 35 cases of posterior uveitis which are charted in Table 10, 14 were treated with cortisone systemically, and only three of the eyes failed to improve. Two of these unimproved eyes were later improved with fever therapy.

The 11 eyes which did improve following systemic cortisone did so gradually. One of these cases relapsed, but now remains quiet with cortisone drops. Of the eight cases

which were treated with cortisone injected into the retrobulbar space, four were improved.

Thirteen of the cases were treated with cortisone locally; two of these improved but these two cases were treated with subconjunctival and drop therapy over a long period of time, and time itself may have been instrumental in effecting improvement.

SYMPATHETIC OPHTHALMIA

The results of cortisone therapy in cases of bilateral diffuse uveitis following uveal tract surgery or trauma are tabulated in Table 11. In six of these cases, one of the eyes has been enucleated. Study of the globe

TABLE 5
OCULAR CONDITIONS TREATED WITH CORTISONE

Diagnosis	Etiology	Mode of Therapy				Number of Eyes	Improved	Unimproved	Relapsed
		Subconjunctival	Drops	Systemic	Retrobulbar				
Macular degeneration	Juvenile			1	1	2		2	
Macular degeneration	Senile	1	1	6	1	8	1	7	
Retinitis pigmentosa	?	1		2		2		2	
Eales's disease	Tuberculous?			2		2		2	
Retrobulbar neuritis	Multiple sclerosis			2	4	6		5	1
Retrolental fibroplasia	?	2		2		4		4	
Central serous retinitis	?			2		2		2	

TABLE 6
SUMMARY OF RESULTS OF CASES TREATED
WITH CORTISONE

Number of Eyes Treated*	344
Mode of Therapy	
Subconjunctival	236
Drops	108
Systemic	52
Retrobulbar	14
Results	
Improved	168
Unimproved	120
Relapsed	35

* 22 treated eyes were reported but not tabulated

TABLE 7
CONDITIONS DEFINITELY IMPROVED BY CORTISONE
ACETATE AS ADMINISTERED IN THIS STUDY

I. Infections	Bacterial—Blepharitis Drug sensitivity Episcleritis
II. Possible allergic states	Superficial keratitis Nonlucetic interstitial keratitis Uveitis

TABLE 8
CONDITIONS IN WHICH CORTISONE AS USED IN
THIS STUDY IS OF QUESTIONABLE VALUE

I. Infections	Viral—Dendritic keratitis herpes zoster
II. Possible allergic states	Deep corneal ulcers Sclerosing keratitis Vernal conjunctivitis Marginal corneal ulcers
III. Chemical burns	Lime

TABLE 9
CONDITIONS NOT IMPROVED BY CORTISONE AS
ADMINISTERED IN THIS STUDY

I. Infections	Bacterial—Uveitis due to brucellosis Possibly bacterial—Uveitis; Sarcoid Possibly viral—Vogt-Koyanagi; Harada
II. Possible allergic states	Luetic interstitial keratitis Erythema multiforme Ocular pemphigus Eales's disease Central serous retinitis
III. Unknown etiology	Ring abscess of the cornea Corneal dystrophy Retrobulbar neuritis Macular degeneration Retrolental fibroplasia

has established the diagnosis of sympathetic ophthalmia in five of the eyes.

Of the 16 eyes, seven were treated with cortisone locally and three of these were improved with no further treatment. One of the eyes was improved but relapsed when therapy was discontinued. It improved again with more therapy and is now quiet with the use of cortisone drops. In these four cases the inflammatory process was diffuse, but most marked in the anterior segment.

In the three cases that were unimproved with subconjunctival cortisone therapy, the uveitis was more severe and largely confined to the posterior segment. Of the nine eyes that were treated with systemic cortisone therapy, two were unimproved. These two cases which did not improve failed to benefit from any other form of therapy.

Five of the cases described in Table 11 relapsed each time cortisone therapy was discontinued. These patients are required to use cortisone solution drops, one drop in the affected eyes at least two to three times a day, in order to keep the inflammatory process quiet.

It is interesting to note that, in some cases, in the presence of any mild illness such as an upper respiratory infection, the need for the drops is increased and patients have learned to regulate the frequency of the use of the drops to correspond to the situation.

Those cases of bilateral diffuse uveitis following surgery or trauma which were treated with systemic cortisone received this therapy for a period no longer than 14 days. Local cortisone in those cases which did not relapse was required from eight to 21 days. One of the cases which tends to relapse has received cortisone drop therapy intermittently over a 10-month period.

One cannot always be certain of the diagnosis of sympathetic ophthalmia, but there was definite improvement in the sympathizing eye of the cases that had been diagnosed by histologic examination of the exciting eye.

TABLE 10
POSTERIOR UVEITIS
(nonspecific)

Type of Therapy	Number of Eyes		
	Im- proved	Unim- proved	Re- lapsed
Subconjunctival cortisone	2	9	
Cortisone solution-eyedrops	0	2	
Systemic cortisone	7	2	
Combination: Systemic and local cortisone	3	1	1
Retrobulbar cortisone	4	4	
Summary			
Systemic therapy	10	3	1
Local therapy (including retrobulbar)	6	15	
Number of eyes treated—35.			

TABLE 11
BILATERAL DIFFUSE UVEITIS FOLLOWING SURGERY
OR TRAUMA TO THE UVEAL TRACT
(Sympathetic ophthalmia?)

Type of Cortisone Therapy	Number of Eyes		
	Im- proved	Unim- proved	Relapsed
Local	3	3	1
Systemic	2	2	5
Total	5	5	6
Total number of eyes treated:		16	
Improved:		5	
Improved, then relapsed, with improvement continued with cortisone drops:		6	
Unimproved:		5	

HYPERTENSIVE UVEITIS

Sixteen cases of anterior uveitis with secondary glaucoma were treated in this series. The results obtained are outlined in Table 12. Of the 16 cases the glaucoma was

controlled in only nine cases. In three of these, the glaucoma had not been controlled with mydriatics and hot compresses. This had been the only form of therapy for two to three days prior to the beginning of corti-

TABLE 12
ANTERIOR UVEITIS WITH SECONDARY GLAUCOMA

Case No.	Type of Therapy			Results
	Subcon- junctival	Drops	Sys- temic	
1	X			Glaucoma not controlled
2	X			Tension controlled. Uveitis relapsed but improved with further therapy and is now quiet with cortisone drops t.i.d.
3	X			Glaucoma not controlled. No improvement with cortisone or any other method of therapy
4	X			Glaucoma controlled by cortisone after mydriatics alone had failed
5	X	X		Glaucoma controlled
6	X	X		Glaucoma controlled
7		X		Glaucoma controlled. Uveitis relapses when drops are discontinued
8	X			Glaucoma not controlled. Uveitis due to brucellosis. Good response to streptomycin and aureomycin
9	X	X		Glaucoma not controlled. No improvement with cortisone or any other method of therapy
10	X	X	X	Glaucoma developed while patient was being treated with cortisone topically. Systemic cortisone did not improve the glaucoma or the uveitis
11	X	X		Glaucoma not controlled. No improvement
12	X			Glaucoma controlled. Improved
13	X			Glaucoma not controlled. Glaucoma had been present 2 weeks
14	X			Glaucoma controlled. Improved
15	X			Mydriatics had been used 3 days with no improvement. Glaucoma controlled within 12 hours after onset of cortisone therapy
16	X			Mydriatics had been used 2 days with no control of the glaucoma. Glaucoma controlled within 12 hours after cortisone therapy began
Summary				
Number of eyes improved				— 9
Number of eyes unimproved				— 7
Number of eyes treated				— 16

sone therapy. In three of the cases the intraocular pressure was within normal limits 12 hours after the use of local cortisone.

Cortisone was administered subconjunctivally in all but one of these eyes, and in this eye cortisone drops were employed. Of the seven eyes which did not respond to cortisone, five were unresponsive to any other therapy. One case of uveitis with secondary glaucoma thought to be due to brucellosis was improved when streptomycin and aureomycin were administered systemically.

CORTISONE FAILURES

Table 9 lists those conditions which were not improved with cortisone. It is apparent that many of these conditions are degenerative rather than inflammatory.

Of the 10 cases of macular degeneration only one was improved. This case is interesting in that in one eye the macula was seriously damaged due to degenerative changes that had their onset three years previously. The patient was admitted to the hospital with the complaint of diminished vision in the previously uninvolved eye. The macula in this eye revealed early changes consisting of edema and irregularity of pigmentation. After 1,000 mg. of cortisone had been given systemically, the macula appeared less edematous and the vision was improved from 6/30 to 6/9. This improvement has been maintained with no further therapy for six months.

RETROLENTAL FIBROPLASIA

The four eyes with retrolental fibroplasia which were treated in this study were in the cicatricial stage and were more seriously involved than were the eyes treated with ACTH by Reese and Blodi, and others.^{18-a, b} The eyes in this series were not improved.

CORTISONE AND SURGERY

Nine cases, which are not tabulated, were given cortisone subconjunctivally before sur-

gery. These cases were subject to recurrent attacks of uveitis but they were quiet at the time the cortisone was injected prior to the surgery. It was hoped that the cortisone would block a possible recurrence of the inflammatory state during the postsurgical period. In another similar case, 475 mg. of cortisone were given systemically before surgery. In none of the 10 cases was there any recurrence of the uveitis during the hospitalization following the intraocular surgery. However, this may or may not have been due to the cortisone therapy. It is noteworthy that wound healing was uneventful in each of these cases.

CORTISONE AND SEVERE OCULAR TRAUMA

Twelve eyes which had been severely traumatized were treated with cortisone in this study. These cases are not tabulated since results of therapy cannot be evaluated. In this group, nine of the cases had had severe lacerations of the cornea and/or sclera and there were intraocular foreign bodies in the other three eyes.

Concurrent therapy in these cases included antibiotics, fever therapy, atropine, and hot compresses where indicated. With such an extensive use of other forms of therapy it is impossible to evaluate the use of cortisone in these cases.

Eleven of the eyes quieted but appeared to do so no more rapidly than had cortisone not been used. One of the eyes developed endophthalmitis and was enucleated. Sympathetic ophthalmia did not develop in any of these cases. All of these eyes received reparative surgery. In no case was there evidence of delayed wound healing.

CORTISONE AND FEVER THERAPY

There were nine eyes in this series that were not helped by previous fever therapy which did respond favorably to cortisone. It has been suggested that cortisone and fever therapy have some common physiologic ef-

fects.¹⁷ The results obtained in these nine eyes and in the two cases which responded to fever therapy after cortisone had apparently produced no improvement, may suggest that the actions of cortisone and fever are not identical.

Fever therapy may not mobilize adrenocortical steroids to equal the concentration obtained by injected cortisone. This might account for the superiority of cortisone over fever therapy in the nine eyes that were not helped by fever therapy, but not for the superiority of fever therapy over cortisone in the two eyes.

DISCUSSION

From the results obtained in the cases treated in this series and those obtained in the series reported by Haik and Waugh²⁴ and others, one may conclude that cortisone used systemically is the treatment of choice in sympathetic ophthalmia. Haik and Waugh report that many cases which are diagnosed as sympathetic ophthalmia are probably cases of endophthalmitis phaco-anaphylactia. Fortunately cortisone has been used successfully in the treatment of both of these conditions, so that the differential diagnosis is not imperative therapeutically.

Cortisone used locally improved three of the cases which were thought to be sympathetic ophthalmia. However, the more severe cases and those in which the exciting eye was proven to be sympathetic ophthalmia were improved by systemic cortisone.

Thorpe²⁵ reports that, in 10 cases of severe ocular trauma, cortisone or ACTH had improved or prevented traumatic uveitis and failed to hinder wound healing. In 12 similar cases in this series, no severe complications developed and there was no delay in wound healing.

Ten cases, subject to recurrent uveitis, had been given limited quantities of cortisone preoperatively. No more was given than a total of 15 mg. subconjunctivally to each of

the nine eyes and 475 mg. systemically to one patient. There was adequate wound healing in each of these cases. Apparently cortisone will interfere with wound healing only when given in amounts greater than were used here.

The ages of these 10 patients who were subject to recurrent attacks of uveitis ranged from 30 to 83 years. Most of the cases were in the 60- to 83-year age group. The patients who had had severe ocular trauma with no interference with wound healing with cortisone therapy were in the 30- to 50-year age group.

One might presume that the older patients would be more unfavorably influenced insofar as wound healing is concerned when cortisone is used than would younger patients. From the results obtained in this study, it appears that age is not an important factor in wound healing in the presence of cortisone.

CONCLUSIONS

1. Glaucoma secondary to uveitis may respond to local cortisone if the uveitis is quieted.
2. Topical or systemic cortisone may block a recurrence of uveitis after intraocular surgery without interfering clinically with wound healing.
3. Topical cortisone is of benefit in many inflammatory and allergic diseases affecting the lids, conjunctiva, sclera, cornea, and the anterior segment of the globe.
4. Systemic cortisone is beneficial in cases of phaco-anaphylactia, sympathetic ophthalmia, and other inflammatory or allergic processes affecting the uveal tract.
5. Some cases treated with cortisone tend to relapse when therapy is discontinued.
6. Cortisone does not appear to be helpful in degenerative diseases of the eye.

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THE SULFONAMIDES AND ANTIBIOTICS IN TRACHOMA*

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INTRODUCTION

The role of the sulfonamides and antibiotics in medicine generally is well established. In ophthalmology, these new agents have greatly increased the amplitude of ophthalmic therapeutics. The sulfonamides have been found to be decidedly effective in pyogenic infections of the eyelids, eyeball, and lacrimal apparatus; also in streptococcal, pneumococcal, and gonococcal infections; in many other mixed infections, and again in some virus infections.

More dramatically, the antibiotics too have displayed a decided specificity for the infectious conditions mentioned, showing an even greater degree of effectivity in many cases that were particularly resistant to treatment by sulfonamides.

In trachoma, however, we must consider a chronic disease which is fairly resistant to treatment generally. It is believed to be caused by a small virus or rickettsial body (Prowazek's cell inclusions) and produces a prolonged period of illness wherein the end point is not well defined.

If unchecked or permitted to progress with only desultory treatment, the disease will result in cicatricial complications that affect both the eyelids and globe, and which are not readily resolved by treatment of any kind. Moreover, the stage at which trachoma ceases to be infectious is still a factor surrounded with some doubt.

The infectious agent, too, soon after invasion, penetrates the subconjunctival layers of tissue and is difficult to reach with ordinary methods of bactericidal agents. Yet, the disease remains throughout a strictly local-

ized affair; and, except for involvement of the entire conjunctiva and its reflections and extensions over the anterior segment of the globe, it never invades the eyeball itself nor extends into the realm of other adnexal tissues.

For these reasons, trachoma presents etiologic, clinical, and pathologic characteristics not encountered in the ordinary run of conjunctival and corneal afflictions and, therefore, it seemed desirable to study the new therapeutic agents over a long period of clinical trial before a satisfactory evaluation of their effects and results could be concluded.

CLINICAL TRIAL

To this end, the following named preparations were put to clinical trial and the results observed in a series of over 3,500 patients at the Missouri Trachoma Hospital during the decade 1941 to 1951:

Sulfanilamide, sulfapyridine, sulfathiazole, sulfathiazine, albucid (sulfacetimide), sodium sulfacetimide (albucid soluble), sulfamylon, Combisul (sulfadiazine, sulfamerazine and sulfathiazole combined), Gantrisin, penicillin, bacitracin, streptomycin, chloromycetin, aureomycin, and terramycin.

Some of the sulfonamide drugs were used in tablet form for internal medication, and some in aqueous solution used as drops for local instillation into the conjunctival sac; both these methods being combined with use of the drug in ointment form for overnight application.

The antibiotics were prepared as fresh buffered, aqueous solutions daily from the crystalline powders supplied in sterile vials and used for topical application every two hours. Bacitracin and terramycin ointment, 500 units per gm., was used as an overnight coating for the conjunctiva. No intramuscular or intravenous injections were tried.

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Only surface applications of antibiotics were used since it had been reported (Miller¹) that systemic injections of adequate dosage do not produce measurable concentrations of these drugs in the ocular (particularly conjunctival) tissues and fluids. Moreover, I felt that in cases of trachoma, at least, subconjunctival injections of antibiotics were not justifiable since simpler methods appeared as effective. Although either local or systemic injections are indicated in cases of intraocular, orbital, and uveal infections, in trachomatous conjunctivitis and keratitis, however, this form of therapy does not seem to be warranted.

In trachoma, the ideal therapeutic agent should be one that combines specificity of action and speedy effects with bland or mild action when used locally on the cornea and conjunctiva. The older, harsh methods of treatment for this disease possessed none of these ideals; for instance, the silver and copper salts in various concentrations applied directly to tissue were not only nonspecific for the trachoma virus, but caused pain and discomfort to the patient, prolonged the period of treatment by traumatizing delicate membranes, and added to the cicatrization already present or on its way.

Argyrol in various strengths from five to 20 percent, protargol, and other silver-protein preparations of recent years enjoyed a wide popularity, but resulted more often in staining of the conjunctiva (argyrosis) than in an amelioration of the disease. Other therapeutic agents of time-honored use were chaulmoogra oil, tartar emetic, quinine bisulfate, mercury perchloride, lead acetate, carbolic acid, acetic acid, glycerine, trachocid, and many others too numerous to mention.

The early sulfonamides used about 10 years ago, however, were found to be generally bland in action, nonirritating to the patient, nonscar-forming, and somewhat specific in action against the trachoma virus. Because these solutions or salts were unable to be concentrated sufficiently for intensive local action, treatment was usually very pro-

longed. Further, toxic side reactions were not infrequent and resulted in discontinuation of the drug.

For these reasons, the earlier salts such as sulfanilamide, prontosil, albucid, sulfathiazole, and sulfadiazine did not prove ideal; but up to about 1945 were used almost exclusively at the Missouri Trachoma Hospital because they produced the quickest recovery with the least injurious effects.

The usual routine was to administer drops of saturated aqueous solutions² into the conjunctival sac hourly during the daytime, with tablets per os for internal medication during the first week or 10 days after starting treatment, both drops and tablets being given concurrently.

SULFANILAMIDE

The early results with sulfanilamide (about 1941 to 1942) were generally more satisfactory than with any previous routine of treatment. Locally, the conjunctival inflammation showed early subsidence, turbescence was lessened, and photophobia improved quickly. Discomfort to the patient was lessened. The former use of the silver, copper, and zinc preparations had caused many to complain of the "hot shots" and of the burning and stinging of the conjunctiva following such administration.

Side effects were fairly common, since sulfanilamide was also used internally at this time. Only occasionally did a sensitive individual complain of mild reactions from the drops, such as flushing of the face or mild swelling of the conjunctiva and eyelids.

SULFACETIMIDE

Because of reports in the literature that internal administration of sulfanilamide was not a safe procedure, a need was felt for a sulfonamide drug that would be as efficacious as sulfanilamide, or more so, but without deleterious side effects. To this end albucid (sulfacetimide) was used experimentally, both internally (tablets 0.5 gm., dosage 45 gr. per day) and locally in solution (satu-

rated) as eyedrops. It showed no dramatic improvement over sulfanilamide and was discarded, after several months' use, during the summer of 1941.

SULFATHIAZOLE

Sulfathiazole was tried next in a five-percent solution and also as a pulverized solid dropped directly into the lower cul-de-sac every two hours. The powder formed an insoluble precipitate which remained as such in the conjunctiva, and proved to be of no greater efficacy than the sulfanilamide solution (0.8 of one percent) used previously. Furthermore, the administration of the powder was laborious. The five-percent solution also was found to be of little value.

These, therefore, were discarded for local use. For internal administration, sulfathiazole in 0.5 gm. tablet form was readily accepted, however, because of its relatively low toxicity in comparison with sulfanilamide.

During 1942, the chosen routine in the use of the sulfonamides became: (1) Sulfanilamide saturated, used locally for irrigation and as drops, every two hours, in the conjunctival sac, and (2) sulfathiazole (0.5 gm. tablets) given internally, four to eight tablets per day (adult dosage) for one week to 10 days, both given concurrently. For children, about half the tablet dosage was administered, depending upon age and weight. An equal amount by weight of sodium bicarbonate was taken with the sulfathiazole, for alkalization, in every case.

On this routine, few drug sensitivities were encountered, these consisting of nausea and headaches, flushing of the face and neck, the occasional appearance of a skin rash, and a feeling of anxiety in the patient. These symptoms quickly disappeared upon stoppage of the drug.

SULFADIAZINE

During 1943, sulfadiazine supplanted sulfathiazole as the agent of internal medication. Preference was given to sulfadiazine because it was the less toxic drug and was

found to cause fewer allergic manifestations. It was administered in 0.5-gm. tablets, given four times per day by mouth, in dosage of six to nine tablets per day, depending upon patient's age and weight.

Up to 1945, the latter procedure of treatment (sulfanilamide solution locally and sulfathiazole tablets per os) was found to be most beneficial in trachoma, and was adopted for general use. Over 1,000 cases² of patients hospitalized at the Trachoma Hospital, of all age groups and of both sexes, were studied. In early or beginning cases, in moderately and markedly advanced cases, with or without pannus, and even in late cases with cicatrization, entropion, and corneal ulceration, results proved to be generally beneficial.

In the late cases, however, it was necessary to give auxiliary treatment in the form of pontocaine, atropine, heat, cautery, and intravenous administration of typhoid (non-specific) vaccines for the attending uveitis. To date, such supplemental treatment becomes a necessity in those cases in which complications have become destructive to the tissues of the eye, and call for immediate remedial local treatment with nonsulfonamide ophthalmic reagents.

Surgery is also indicated in various cases: entropion operation to correct the incurvation of the eyelids, epilation for trichiasis, and grattage to remove the exuberant follicular growths on the conjunctiva in order to stimulate healing and repair. This phase of trachoma treatment will not be discussed here, however, as it does not fall within the province of this paper.

NEWER HIGHLY SOLUBLE SULFONAMIDES

SODIUM SULFACETIMIDE

During 1946, a new sulfonamide solution known as sodium sulfacetimide⁴ (Schering Corporation) was tried at the Missouri Trachoma Hospital. This was originally supplied as a 30-percent solution and afforded a greater concentration of sulfonamide solid in solution than any other type of sulfonamide.

However, this high concentration was found to be too irritating for use in trachoma.

Many patients complained of a burning and stinging sensation and, in many observed instances, the congestive signs of local inflammation appeared to be increased instead of decreased. In a number of trachoma patients, the discomfort that followed use of this drug (in 30-percent solution) became so intense that it was necessary to stop its use entirely.

Various dilutions were tried until it was found that the 10-percent aqueous solution produced a maximum of results with a minimum of irritation to the ocular tissues. Sulfanilamide saturated solution (0.8 of one percent) locally was, therefore, supplanted by sodium sulfacetimide (10 percent) solution.

The effects of sodium sulfacetimide were noted for a period of one year or more, both when used alone as local drops and irrigations and when used in conjunction with sulfadiazine tablets taken internally. We found the sulfacetimide solution (10-percent aqueous) to be very efficacious in the treatment of trachoma, even better than the saturated sulfanilamide solution and sulfathiazole (five-percent solution).

The sulfacetimide produced more rapid subsidence of symptoms (itching, burning, photophobia, blepharospasm) and signs (redness and turgescence of the conjunctiva, active pannus, mild concomitant iritis) and shortened the usual hospitalization period of four to eight weeks to three to six weeks.

In most instances, the new drug was well tolerated locally but there were frequent complaints of itching and burning, which had not been present previous to the instillation of the sulfacetimide. In these instances, the drug had to be discontinued because no improvement would follow from prolonged use and the eyes would remain reddened, inflamed, and bothersome.

In a few individuals, marked toxicity of the drug was noted, when used locally in the conjunctival sac, with or without sulfadiazine

medication by mouth. Several male patients, aged between 25 and 40 years, showed a marked local and general reaction after the use of this new drug. The face, neck, and body became covered with an itching, erythematous rash. The conjunctivas became congested, edematous, and chemotic.

These patients were then taken off all sulfonamide drug medication and put on saline irrigations for one week. When symptoms and signs had subsided, the sulfacetimide solution was again tried, locally, without sulfadiazine by mouth, and there followed a recurrence of the side effects to the same degree of intensity.

In other patients sulfacetimide therapy caused milder side effects, notably flushing of the face and neck.

With reference to sulfadiazine itself, previously, when used by mouth in conjunction with sulfanilamide drops or instillations locally, no noxious effects that could be noted clinically had occurred. No blood-level determinations were made or hemoglobin readings determined, but degrees of intolerance or sensitivity to the drug were determined only from clinical observation and subjective symptoms. Of course, one must consider that certain individuals may manifest specific drug sensitivity to one or more drugs, which, when used on others in the same given dosage, produce no side effects at all.

Despite these shortcomings, the therapeutic value of sodium sulfacetimide solution (10 percent, locally) in trachoma was considered to be so much greater than that of other sulfonamide drugs previously used, that it was adopted for general use at the Trachoma Hospital. During 1946 and 1947, this sulfonamide was used almost exclusively in the treatment of trachoma at this hospital because the improved curative effects more than outweighed the disadvantages of occasional side reactions and local irritation to the conjunctiva.

GANTRISIN

During April, 1947, a new experimental

sulfonamide preparation was introduced by Hoffmann-La Roche for clinical investigation, termed NU-445⁵ (later named Gantrisin). This preparation was characterized by comparatively high solubility at neutrality. This property⁶ greatly reduced the likelihood of crystalluria and deposition of crystals within the urinary tract.

Gantrisin (3, 4-dimethyl-5-sulfanilamidoisoxazole) is a white crystalline powder, supplied in tablets of 0.5-gm. size for internal medication by mouth. It attacks the same general range of organisms as does sulfadiazine. The lithium salt forms a stable 10-percent aqueous solution for ophthalmic use.

This new drug (Gantrisin), originally designated as NU-445, is not only extremely soluble but has not yet been shown to give rise to any renal irritation or crystalluria, even though the drug is given in doses up to 15 gm. and more daily.⁶

It was desirable to learn if this sulfonamide would produce desirable curative effects in trachoma rapidly and without toxic side reactions caused by other sulfonamide drugs. Accordingly, a series of trachoma patients were put exclusively on treatment with Gantrisin, and the results noted during the 15-month period following. Over 300 patients with early, moderately advanced, and markedly advanced cases, including those with and without complications, were studied.

Gantrisin was used alone as drops and as instillations of the 10-percent solution in the conjunctival sac, and also in conjunction with internal medication of the tablets (0.5 gm.) by mouth.

Since the toxicity of this drug was reported⁶ experimentally to be very low, the dosage in tablets by mouth was made double that of sulfadiazine and sulfathiazole; our patients were given from six to 20 tablets per day, the average adult dose being nine to 15 tablets per day, children about half this amount, depending upon age. In markedly active cases in adults, as many as 10 gm. per day (20 tablets) for seven days were administered.

From the evidence of the Hoffmann-La Roche report,⁶ a blood-level of 10 to 12 mg. can usually be maintained on a daily intake of six to seven gm. (12 to 14 tablets). No sodium bicarbonate was given concurrently, since the need for alkalinization was obviated due to the high solubility of the drug in pH ranges even below 7.0.

Gantrisin was found to be very efficacious in trachoma, producing a fairly rapid recovery from symptoms and a subsidence of inflammatory signs within a reasonably short time (one to three weeks). Mild and moderately advanced cases responded well to treatment with this drug, when used both locally and internally. Markedly advanced cases responded somewhat more slowly but after several weeks of treatment showed definite improvement. As with other sulfonamide drugs, corneal and uveal complications necessitated the use of other ophthalmic agents, as previously mentioned.

The outstanding feature of Gantrisin (NU-445) was found to be its remarkably consistent freedom from toxic side effects. In the series of cases in which this was used, whether in local instillations or in instillations combined with tablets by mouth, there were very few instances of toxicity or of side reactions and, when these occurred, they were always mild. The Gantrisin drops (10-percent solution⁷) were found to be generally bland and nonirritating to the conjunctiva. Rarely did any of our patients remark about discomfort from irritation or stinging when this solution was used.

The tablet dosage by mouth in adults was increased gradually from six tablets per day to nine tablets and then 12 tablets; later this was again cautiously increased to 15 tablets per day. In many instances, a dosage of 18 to 20 tablets per day was maintained for a period of one week.

All internal medications were given for seven days; local instillations were given concurrently during this one week and continued for as long as the patient remained in the hospital, the average stay usually being

from two to four weeks. Of course, advanced cases with cicatricial complications required a much longer period of treatment.

About one out of four patients on Gantrisin tablets complained of mild nausea and headaches after taking a dosage of 15 or more tablets per day. This began on the same day or the day following administration of the tablets and persisted until a day or two following stoppage of the tablets. No skin reaction of any type and no local ocular reaction was observed. Mild hyperpyrexia was manifested in some individuals. In children who were on one half or less the adult dosage, no reactions of any type were noticed.

In no case, however, was the discomfort from nausea, febricula, or headache of such intensity as to warrant complete cessation of the drug. Patients on 12 tablets or less per day did not manifest any appreciable signs or symptoms of sulfonamide reactions at any time and the dosage was standardized to this amount.

COMBISUL

During January, 1948, a new sulfonamide (Combisul⁴) in tablet form was introduced by Schering Corporation. Combisul consists of equal parts by weight of sulfadiazine, sulfamerazine, and sulfathiazole, to make a combined total of 0.5 gm. per tablet. This was given in daily dosage of six to nine tablets per adult, for one week, in combination with sodium sulfacetamide solution (10 percent) used locally as drops into the conjunctival sac.

For a period of six months, Combisul was used experimentally on selected hospitalized patients of the Trachoma Hospital, treatment being started on admission. Recovery was slow but consistent. The efficacy of this sulfonamide was comparable to that of sulfadiazine. No noteworthy side reactions were observed, and we consider its toxicity to be minimal.

SULFACETIMIDE OINTMENT

Since it seemed possible that an emol-

lient coating of some sulfonamide in therapeutic concentration over the ocular surfaces at night while the patient was asleep would be a desirable adjunctive treatment, we used sodium sulfacetamide ophthalmic ointment¹ (10 percent) as routine in all cases receiving sulfonamide treatment.

A liberal coating was applied between the lids following the last drops treatment of the day; this was done nightly for as long as the patient remained on sulfonamide treatment.

Results were fairly satisfactory but somewhat disappointing because many patients complained of irritation and itching during the night. In some cases it was necessary to discontinue the use of sulfacetamide ointment due to such discomfort. No side reactions of any kind were noted, however, from its application.

Gantrisin four-percent ophthalmic ointment, also used routinely for overnight application, was found to be milder on the conjunctiva but otherwise comparable in effect to sodium sulfacetamide.

SULFAMYLON

Sulfamylon⁸ hydrochloride (one-percent solution) was used during 1950 in a series of trachoma cases, but not found to be of any improved effectivity over other sulfonamides already mentioned. Its action produces a mild, stinging sensation to the conjunctiva and it is comparatively free of toxic effects. I would value its efficacy as only slightly better than some of the older sulfonamide solutions and of no decided advantage to Gantrisin or sodium sulfacetamide.

Gantrisin proved to be the most effective, least toxic, and most soothing of the newer, highly soluble sulfonamide solutions, and in my opinion is of first choice over all other sulfonamides.

At the Missouri Trachoma Hospital the present routine of sulfonamide treatment that yields optimum results is:

1. Local instillation every two hours of drops of Gantrisin (4.3 percent aqueous),

buffered, ophthalmic solution, daily for from 10 days to three weeks.

2. Internal medication with Gantrisin tablets (0.5 gm.), or Combisul tablets (0.5 gm.), given per os in four divided daily doses (according to age and weight) for the first seven days.

3. Coating the conjunctival surfaces nightly with 10-percent sodium sulfacetimide or four-percent Gantrisin ophthalmic ointment during the entire period that drops are given in the daytime.

GENERAL RESULTS

The improvement or therapeutic effect noted from the use of the more recent sulfonamides consisted in earlier subsidence of all inflammatory symptoms, a gradual resolution of the pannus, if incipient, and the rapid disappearance of photophobia and blepharospasm. In mild entropion (and trichiasis) there was an unfolding of the beginning incurvation of the eyelids.

Cases with advanced cicatrization of the palpebral conjunctiva, causing distinct incurvation or entropion, did not respond to any treatment by medication, either locally or by mouth. In such cases, the scarring effect was so advanced as to render treatment by drug alone ineffectual.

PANNUS FORMATIONS

Early pannus formations are fairly well resolved by treatment with the sulfonamide drugs. Moderately advanced vascularizations, especially active ones that have invaded the cornea to some degree, will not resolve entirely. After the acute condition has subsided, however, the pannus will have a ghostlike appearance and will show thinning or fading of the vessel walls.

A well-formed pannus of greater than three or four mm. in length will respond very slowly or not at all to treatment of any kind. In such cases, treatment is prolonged and delayed, and the best that can be hoped for is a cessation of further encroachment of the vessel growth upon the cornea and a

gradual thinning of the vascular twigs during recovery so that as much vision as possible is preserved.

Sulfonamide therapy will not restore the cornea to normal condition in the case of dense pannus formation. Once pannus has advanced to the central area of the cornea, there is very little that can be done in the way of treatment to resolve or remove this invasion.⁹

ULCERATION AND OPACIFICATION

The same may be said of ulceration and opacification of the cornea. Treatment will not clear these conditions entirely although some abatement can be expected. Corneal scars and ulcerations respond only so far as the general condition itself improves; therefore, my experience does not permit the conclusion that sulfonamide drugs will specifically heal the corneal ulceration coincident with trachoma.

Recourse must be taken to other therapeutic methods, the use of optochin (0.20 of 1.0-percent solution) and hot, wet dressings of boric-acid solution, hourly, being favored. When indicated, atropine, dionine, and cautery may be of help.

Some improvement of opacification (if recent) has been observed after sulfonamide treatment. Visual tests before and after treatment are an integral part of every patient's record of stay in the hospital. Unless the opacity is an old one and well developed, the improvement in vision shown after hospitalization, although only slight, is definite. This fact convinces us that at least some resolution of corneal opacities in trachoma, whether due to pannus or ulceration, does follow from treatment with sulfonamide drugs.

Never, however, have I seen a well-marked leukoma or generalized pannus formation become resolved by any sulfonamide treatment. Although a few such patients have joyfully reported that they could see better after many weeks of treatment, I have attributed this apparent result mostly to the effect of psychic suggestion.

CICATRIZATION

Once cicatrization of the conjunctiva of the lids and bulb has established itself or become advanced, there is no resolution. The improvement observed in some entropion patients under sulfonamide treatment may be attributed to relaxation of blepharospastic tendencies, and not due to absorption of scar tissue.

For this reason, we see many early cases of mild entropion that will improve on sulfonamide treatment and afterward show no incurvation at all. Cases of long duration, in which the inversion of the lid was occasioned by the destructive effects of scarification, will not yield to medical treatment under any circumstances. They will require surgical correction.¹⁰

THE ANTIBIOTICS

The following antibiotics were used in trachoma during the past five years at the Missouri Trachoma Hospital: Penicillin, bacitracin, streptomycin, chloromycetin, aureomycin, and terramycin.

PENICILLIN

Penicillin¹¹ was used over a six-month period (1945-1946) as a routine treatment on selected trachoma patients of the hospital, both in early and late cases.

The penicillin was given locally by instillation or conjunctival bath every two hours in the form of an aqueous solution of the sodium crystalline salt, in concentration of 1,000 units per cc. Penicillin ointment of the same concentration (1,000 units per gm.) was used overnight. A fresh solution was made up each morning and kept under refrigeration throughout the day.

A series of approximately 100 cases of trachoma was studied, including newly infected individuals and those of long-standing duration.

The results were disappointing. Penicillin has practically no effect in trachoma per se, although it shows marked efficacy for clear-

ing up secondary infections of *Staphylococcus aureus* and *albus*, *Streptococcus* and *Pneumococcus* in the eye.

Cases of trachoma with concomitant blepharitis, purulent blepharitis, and pneumococcal or staphylococcal tear-sac infections responded well and quickly to treatment with penicillin irrigations, usually within a few days, in some cases within a week. However, no improvement of the underlying trachomatous condition itself was observed to follow. No ocular sensitivities were observed.

BACITRACIN

Bacitracin¹² ointment prepared for ophthalmic use, containing 500 units of bacitracin per gm. in a petrolatum base, was used in cases of trachoma over a period of several months.

Bacitracin has no effect on trachoma per se, but, like penicillin, it shows a remarkable effect in clearing up secondary infections associated with trachoma. No sensitivity in patients was observed. Some purulent cases found to be resistant to penicillin seemed to yield to treatment with bacitracin, notably chronic blepharitis of long duration, with or without ulceration.

TERRAMYCIN

Terramycin¹³ ophthalmic ointment, containing terramycin one mg. per gm., yielded results comparable to bacitracin, that is, generally negative to trachoma but positive to secondary invaders. No sensitivity reactions were noted.

STREPTOMYCIN AND CHLOROMYCETIN

Streptomycin¹⁴ and chloromycetin¹⁵ were used during 1949 in fresh, aqueous solutions prepared daily from the crystalline powders supplied in sterile vials. Streptomycin was used in concentrations of 10 mg. per cc., and chloromycetin in concentrations of 25 mg. per cc. As was the case in penicillin and bacitracin, no specific effects on trachoma

itself were observed, although for clearing secondary infections the results were excellent.

TERRAMYCIN AND AUREOMYCIN

Terramycin¹⁶ and aureomycin,¹⁷ each in 25 mg. per five cc. solutions, were used during 1950 and prepared in the same manner as other antibiotics. The dry mixture of terramycin or aureomycin and appropriate sodium borate-sodium chloride buffers were prepared for topical, ophthalmic use. Solutions were isotonic with lacrimal fluid and buffered to pH 8.2. Fresh, aqueous solutions were used daily for local instillation into the conjunctival sac.

Aureomycin and terramycin were also given internally per os in capsule form, concurrently with drops of the freshly prepared solutions used locally. Six to eight capsules (250 mg. per capsule) was the daily dose.

Results were generally negative for trachoma, and comparable to those of previous antibiotics used.

No sensitivity reactions, ocular or systemic, were observed with the use of the antibiotics, and in general their action on the conjunctiva was mild and soothing.

GENERAL RESULTS

Trachoma patients treated with antibiotic solutions instilled locally every day for several weeks and longer failed to show any improvement in clearing of early pannus, relief from turgescence of the retrotarsal fold, resolution of granules, or even from the increased lacrimation and itching that is almost always present in all trachoma.

Very purulent secretions cleared remarkably within a few days after treatment with antibiotics generally, but in no case could relief from symptoms be traced to improvement of the basic trachoma infection. When secondary infection complicated trachoma, the antibiotics relieved the symptoms somewhat and produced a partial subsidence of inflammation. In such cases, the underlying trachoma seemed improved but this was only

because the superimposed infection was alleviated and controlled.

In each case, the antibiotics as specifics in trachoma were found to be disappointing. Even the later discoveries—chloromycetin, aureomycin and terramycin—appear to have no effect in trachoma per se. This is surprising when we consider the effectiveness of antibiotics in other diseases of viral origin, such as measles, mumps, influenza, herpetiform diseases, typhus, and Rocky Mountain spotted fever.

Since they show a marked efficacy for clearing up ocular infections of *Staphylococcus aureus* and *albus*, *Streptococcus*, *Pneumococcus*, and *Gonococcus*, cases of trachoma with concomitant blepharitis and purulent blennorrhoeas responded well and quickly to treatment by irrigation, usually within a few days, in some cases within a week.

Very purulent secretions cleared almost immediately to penicillin, bacitracin, aureomycin, and terramycin. Trachoma complicated with pneumococcal or staphylococcal tear-sac infections required longer treatment. When such secondary infection was the predominant cause of the patient's conjunctival inflammation and discomfort, as is sometimes the case in trachoma here and almost always in the Orient,¹⁸ the antibiotics relieved the symptoms and produced a rapid subsidence of inflammation. However, in all such cases of concurrent infections, no improvement of the underlying trachomatous condition itself was observed to follow.

Since antibiotics were found to be very effective in clearing common secondary infections concurrent with trachoma, they may be said to be valuable as an adjunctive treatment in this disease. Cases of trachoma that enter the Missouri Trachoma Hospital for treatment and which are markedly infected with secondary purulent secretion are first put on antibiotic instillations for several days until the purulent secretion disappears and the general inflammatory signs decrease somewhat.

DISCUSSION

There has been considerable controversy during the past decade as to whether or not the sulfonamides have a specific effect on the virus of trachoma. The majority of investigators claim they do have a specific effect and base their claims upon clinical observations.

Thygeson¹⁹ points out that in cases in which specific inclusion bodies were found previous to the internal administration of sulfanilamide, they could not be found after treatment with this drug. Other investigators²⁰ have demonstrated that the Halberstaedter-Prowazek inclusion bodies disappear from the conjunctiva in a period of a few days or more following sulfonamide treatment, and after 10 days in the great majority (80 percent) of cases.

Sorsby²¹ concludes from his observations that the sulfonamides are indeed specific against the virus of trachoma, and not merely against any associated secondary infection.

I am in agreement with the conclusions of these investigators, and it is my opinion that further bacteriologic study will conclusively prove specificity for sulfonamides in trachoma.

The antibiotics, too, have come under discussion recently with regard to specificity for trachoma. Freyche²² has presented an excellent review of the literature on the various results of antibiotics in trachoma, and from his discussion one may assume that the question of specificity of certain antibiotics for this disease is still in much doubt.

I am in agreement with this writer that a long time must elapse before it becomes possible to decide whether or not any agent is the specific drug for trachoma, what are the best methods of administration and the optimum dosage; and, if I may add, which drug will universally treat all races of trachoma peoples successfully.

It is my opinion that different racial characteristics and conjunctival flora may materially affect the symptomatology of trachoma to such an extent that different dos-

ages, different methods of administration, and even different therapeutic agents may be necessary to combat this disease in various areas.

Of all the antibiotics tried here and abroad, aureomycin and chloromycetin seem to be most favored as specifics in trachoma. Some observers²³ believe these agents will cure trachoma in an incredibly short time, even bringing about the resolution of opacities and clearing of pannus. One wonders if these results were based not upon actual trachoma abatement, but upon the overall beneficial effect from removal of superimposed infection.

On the other hand, the opinions of Bietti²⁴ and his associates, based upon clinical experiments in the ophthalmic clinic of Pavia, are tempered with much more conservatism regarding the dramatic effect of aureomycin and chloromycetin. These investigators considered that the results obtained had not proved unquestionable superiority of these antibiotics, but they appeared to be of some value when used in a limited number of observed cases, and notably in clearing of conjunctival flora in a few days.

As stated previously, trachoma in this country, as well as that in Europe and the Orient, is very often secondarily infected, usually with purulent organisms, for which antibiotics exert a marked curative effect. In Egypt, for instance, trachoma is almost always secondarily infected with gonococci or Koch-Weeks infection, or with other purulent organisms.²⁵

Very often, trachoma is preceded by one of these conditions, or, mixed infections are concurrently present and sometimes one will rise to prominence while the other is subsiding. Since antibiotics generally are very effective against these infections, a rapid improvement of the overall clinical picture results, and the credit is given essentially to trachomacidal action instead of more properly to abatement of superimposed infection.

One sees, then, that it would not be too difficult to draw premature conclusions re-

garding specificity of action for aureomycin and other antibiotics in the treatment of this disease, attended as it so often is with many different types of organisms.

Changed symptomatology may be another explanation for the belief of some observers, notably our foreign colleagues, that antibiotics are specific against the ultravirus of trachoma. In the Orient trachoma presents a somewhat different clinical picture from that of the native whites in America. In the latter, the disease is manifested by severe and devastating signs and symptoms, immobilization of the patient, and very often results in much suffering and blindness.

Among Orientals, the disease is more generally widespread but is less severe both as to symptoms and resulting complications.²⁶ Perhaps in Orientals certain racial and immunologic factors are present, as this disease is with them an ancient affair; whereas, in America, trachoma is historically very young, not quite 200 years old if we trace infection back to the landing of the immigrants during colonial days.²⁷

From this, it is reasonable to assume that, when a particular infectious agent is removed from one habitat to another and harbored in the conjunctival tissues of a different race, in a different climate, a change in virulence may occur; or, as is believed to be the case here, a different degree of tissue reaction on the part of the host may occur. In other words, varied susceptibility and varied immunologic aspects must be considered.

Perhaps antibiotics may react more effectively on the trachoma virus that is symbiotic with the particular conjunctival flora of one area in the world, such as the near-East, Egypt, and India, for example, and yet be ineffective on the trachoma virus associated with conjunctival flora of a different race and climate.

Undoubtedly, the virulence of the trachoma virus is not changed, for, when trachoma passes from the conjunctiva of an Oriental to that of an Anglo-Saxon, more devastating

effects and increased suffering are noted.

Wilson²⁸ believes that, in Egypt, trachoma reacts differently from that among Europeans, and that the tendency toward spontaneous cure is much more evident among Egyptians than among Europeans. He further believes that the lesions of trachoma are mild and that suffering is little among Egyptians in comparison to trachoma among Europeans. He believes that this is due to a relative degree of inherited immunity and not due to loss of virulence.

I am in agreement with these beliefs, and it seems reasonable to assume, furthermore, that the varying symptomatology among races is conditioned by the inherent conjunctival flora and the changed tissue reaction of the racially new host.

SUMMARY AND CONCLUSIONS

The sulfonamides generally have proven their positive efficacy, if not outright specificity, in trachoma. They are used as first therapeutic choice at the Missouri Trachoma Hospital because of their mildness of action and apparent specificity against the trachoma virus. The newer, highly soluble, nontoxic sulfonamides of recent years are particularly effective and have been shown to produce more rapid recovery and greater effectivity than the older drugs.

Sulfonamide solutions, used as drops in the conjunctival sac, have proved to be more effective than tablets used alone internally by mouth. It appears that a combination of sulfonamide drops instilled locally and tablets given internally yields the best therapeutic results.

The following sulfonamides are named in order of their efficacy in trachoma:

Gantrisin solution (4.3 percent), sodium sulfacetimide solution (10 percent), sulfamylon (one percent), sulfanilamide solution (0.8 of one percent), sulfathiazole solution (five percent), and powdered sulfathiazole.

Because of their physical and chemical properties, Gantrisin and sodium sulfaceti-

mide solutions seemed to be best suited for local use in trachoma. Aqueous, buffered, ophthalmic solutions in five to 10-percent concentration seem to be optimum density for effectivity and yet retain blandness of action on the conjunctiva.

Internal medication by mouth with sulfathiazole, sulfadiazine, sulfapyridine, Combisul, and Gantrisin (NU-445) has proved to be of adjunctive value when given in combination with sulfonamide solutions used as drops. When these drugs were given internally, alone without drops, they proved to be of only slight efficacy. With regard to sensitivity reactions, sulfadiazine, Combisul, and Gantrisin showed least toxicity and were found most satisfactory.

The antibiotics penicillin, bacitracin, chloromycetin, streptomycin, terramycin, and aureomycin have no effect on trachoma itself, but, for clearing up secondary infections usually concurrent with trachoma, they show a marked efficacy and thus serve to shorten the total morbidity period of this disease.

Corrective surgery is usually performed after the initial course of sulfonamide therapy is completed. Even those cases which

seem to indicate immediate surgery on first examination (as in marked entropion with distichiasis) usually improve somewhat when placed on sulfonamide treatment until ready for operation. This procedure clears the infected area of turgescence and swelling, thereby paving the way for a cleaner operative field. It also helps to decrease postoperative discomfort.

The *primary* role of the sulfonamides in the treatment of trachoma is established. Antibiotics are of *secondary* help in clearing the common pus-producing organisms attendant to trachoma.

During the past decade sulfonamides have been used successfully for local and systemic medication, showing results that are truly remarkable.

Although therapeutic agents which give speedier effects and possess greater flexibility would be desirable for use in trachoma and in secondary infections concurrent with trachoma, to date the sulfonamides stand superior to all other therapeutic agents, and are particularly to be preferred to the older and harsher methods of treating this disease.

The Missouri Trachoma Hospital.

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5. This compound (NU-445), in the form of the lithium salt, was generously supplied to me in 1947 for this clinical investigation by Hoffmann-La Roche, Inc., Nutley, New Jersey.
6. From brochure of descriptive data on NU-445 by Hoffmann-La Roche, Inc.
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THE USE OF HYALURONIDASE IN OPHTHALMOLOGY*

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REVIEW OF LITERATURE

The enzyme, hyaluronidase, was discovered in pneumococci by Meyer, Dubos, and Smyth¹ in 1936. This was later found by Chain and Duthie² to be the spreading and diffusing factor which was present in cattle testes. They found that the testicular mucinase would act on the polysaccharide, hyaluronic acid, in the vitreous humor, which was described by Meyer and Palmer in 1934.³

Since the properties of mucinase were identical with those of the spreading factor and since the occurrence of the spreading factor in bacterial filtrates had been found to go parallel with their mucinase content, they concluded that the mucinase and spreading factor were identical. The spreading action of hyaluronidase is therefore accompanied by depolymerization of hyaluronic acid.

The earlier studies on hyaluronidase and its properties were reviewed by Atkinson⁴ who reported on its use with local anesthesia in ophthalmology. This was followed by other reports by Lebensohn,⁵ Key,⁷ and Linn and Ozment.⁸

Atkinson⁴ reported on the diffusing property of hyaluronidase chiefly with anesthetic solutions. He used the preparation hydase (Wyeth) in 109 preoperative injections of an anesthetic solution with such surgical procedures as minor lid operations, cataract extractions, enucleations with implants, operations for glaucoma, retinal detachment, and strabismus.

The results showed that there was a greater diffusion of the anesthetic solution, the anesthesia occurred more rapidly with hyaluronidase, and there was a greater area of anesthesia. More effective akinesia of the orbicularis and extraocular muscles was obtained. After cone injections the hypotony of the eye was pronounced and, although it

* Presented at the third annual conference, Wills Eye Hospital, Philadelphia, March, 1951.

made the cataract extraction slightly more difficult in delivering the lens, the operation was much safer since vitreous loss was less likely to occur. In 20 eyes with a normal pressure averaging 19 mm. Hg (Schiotz) the decrease in pressure ranged from 6 to 9 mm. Hg, five minutes after the injection was given.

Lebensohn⁵ also reviewed some the earlier works and described the properties of hyaluronic acid and hyaluronidase. He employed the triple combination of procaine, epinephrine, and hyaluronidase in over 100 different ocular operations and he also found that akinesia was more marked and prolonged. In enucleations and in tear-sac operations, this method was especially useful.

He found that in a case of glaucoma, the addition of hyaluronidase to the usual procaine-epinephrine solution for retrobulbar injection reduced the intraocular pressure from 46 to 27 mm. Hg in 15 minutes.

He also found that the use of hyaluronidase with retrobulbar injections of 25 to 50 mg. of niacin enhanced the effect of producing vasodilatation when indicated.⁶ In a case of iridocyclitis which did not respond to cortisone drops or subconjunctival injections of cortisone, the preliminary injection of hyaluronidase subconjunctivally, followed in 10 minutes by the subconjunctival injection of cortisone, produced a dramatic effect.

Lebensohn also found that, when hemorrhage occurs after either the subconjunctival injection of hyaluronidase or after retrobulbar injection, it diffuses more widely than usual, probably because of the spreading factor. (I have also found this to be true in cases of subretinal hemorrhage, orbital hemorrhage, and retinal edema following trauma.)

The same author also reported the use of hyaluronidase in the case of hypopyon which disappeared five minutes after the injection and did not subsequently recur.

Lebensohn also suggested the use of subconjunctival injections of 150 t.r.u. hyaluronidase in cases of thyrotropic exophthalmos

and cited one severe case in which three such injections at 24-hour intervals produced an immediate and permanent result after a Naffziger operation had failed.

A case of thyrotropic exophthalmos with glaucoma was, however, reported by Kadin⁹ in which he administered 250 viscosity units of alidase (Searle) which was dissolved in three cc. of two percent procaine. One cc. was injected retrobulbarly, one cc. into the edematous upper lid, and one cc. into the conjunctiva of the lower lid. He found that the use of hyaluronidase in this case increased the edema and proptosis.

The importance of hyaluronidase in glaucoma was the subject of a preliminary study by Linn and Ozment.⁸ It was instilled into the anterior chamber of two patients with secondary glaucoma and a temporary beneficial effect on the intraocular pressure was observed.

Injection of the enzyme in concentrated form into the anterior chamber of rabbits produced clouding of the cornea, keratectasia, and iritis. Histologic studies of enucleated eyes revealed destruction of the corneal stroma, with massive corneal edema, iritis, and congestion of the ciliary processes.

Their results left several questions unanswered. These were concerned principally with degree of purification, degree of sterility of the preparation, and other factors.

SCOPE OF PRESENT STUDY

During the past year I have employed hyaluronidase (Wydase-Wyeth) in about 160 cases of different kinds, 90 of which were cataract cases in which surgery was performed. The other cases included lens loopings, extraocular muscle surgery, enucleations, chalazia, and minor cysts, cases with marked postoperative chemosis and edema, intraocular hemorrhage and retinal edema following trauma, and reduction of intraocular pressure in acute and secondary glaucoma.

In the cataract cases in which surgery was performed, the hyaluronidase was used al-

most routinely in association with procaine and epinephrine for providing akinesia, very much according to the technique described by Atkinson.⁴

Wydase is the purified preparation supplied by Wyeth in small vials containing 150 t.r.u. This is dissolved in one cc. of normal saline solution. About one-sixth cc. of this solution is then removed and added to about three cc. of procaine-epinephrine solution in a separate syringe. The solution of three cc., therefore, contains about 25 t.r.u. of Wydase. The mixture is then injected by either the Van Lint or O'Brien method.

The combination of epinephrine and hyaluronidase with procaine will prolong the anesthesia and accentuate the spreading action. As pointed out by Atkinson, a second injection is never necessary since complete paralysis of the orbicularis can be obtained by this method.

Since hyaluronidase is more effective under slight pressure, gentle massage after the injection is often beneficial. It also prevents formation of a large bleb especially in subconjunctival injections and superficial injections under the skin for removal of chalazia and other minor operations performed under local anesthesia.

I employed retrobulbar injections in cataract surgery, in selected cases only and not as a routine procedure. The hypotony, encountered by others after retrobulbar injection, can be so marked that it renders the corneal section and the extraction of the lens somewhat more difficult.

In my cases, however, it was found that this difficulty could be obviated by making the injection not earlier than five minutes before the corneal section is made. When an eyeball is too soft for a satisfactory corneal section, the injection has probably been made too early. The timing of the injection is apparently an important factor. If the solutions are injected about five minutes before making the section, the degree of hypotony will not be sufficient to prevent a satisfactory section and extraction, while, at the same

time, the eye will prove more safe as far as accidents in the course of the operation are concerned.

This hypotony of the eyeball produced by retrobulbar injection of procaine, epinephrine, and hyaluronidase is of particular advantage, however, in cases requiring removal of the lens by looping. In operations for removal of dislocated lens and those cases in which the possibility of vitreous loss is great because of increased pressure, the use of 25 to 30 t.r.u. of hyaluronidase with procaine and epinephrine for retrobulbar injection, will reduce the intraocular pressure and eliminate almost entirely the danger of such accident.

I have used this method in about 10 such cases with excellent results. The cornea can be laid back with perfect safety and the lens practically lifted out, with no danger of vitreous loss. In patients in whom the use of epinephrine might be contraindicated, procaine with hyaluronidase alone was employed.

The effect of reducing pressure in cases of acute and secondary glaucoma was noticeable in a number of cases but in most of these the pressure would again become elevated after 48 hours. A retrobulbar injection of procaine, containing 25 to 30 t.r.u. of hyaluronidase, would lower the intraocular pressure by Schiötz as much as 10 mm. Hg or more after about 10 minutes.

In postoperative chemosis and edema of the conjunctiva persisting after cataract extraction, 150 units of hyaluronidase instilled into the conjunctival sac will produce almost immediate improvement. In cases of postoperative chemosis and orbital edema, such as occurs at times after enucleation, an injection of 150 t.r.u. will reduce the chemosis and edema almost immediately.

In five cases of orbital hemorrhage due to traumatism, a retrobulbar injection of procaine-epinephrine containing 100 t.r.u. of hyaluronidase was given on two successive days with rapid absorption and disappearance of the hemorrhage with no permanent damage resulting.

Fifty units in three cc. of solution have

also been injected in three cases of retinal edema following trauma. The injection in two cases was repeated on the following day. The edema became diffuse and gradually disappeared within 48 hours.

In minor operations about the eyelids, about 10 t.r.u. Wydase in one cc. of procaine solution will provide excellent infiltration anesthesia for chalazia, small cysts, and other superficial lesions.

CONCLUSIONS

In conclusion it can, therefore, be stated that the results obtained from the clinical use of hyaluronidase in a variety of ocular conditions were found in general to confirm those obtained by others:

1. Hyaluronidase is very useful, in association with procaine and epinephrine, for providing better akinesia with greater diffusion of the anesthetic. In most cases, also, it has a greater effect on the ocular muscles.

2. It is very useful as an adjunct for infiltration anesthesia in minor surgery about the eyelids. It provides better anesthesia and almost bloodless field in these cases, as well as with enucleations.

3. In cataract extraction, a retrobulbar injection of procaine-hyaluronidase, not more than five minutes before operation, will permit a good corneal section and at the same time provide sufficient hypotony to render the operation more safe.

4. Lens-looping operations for dislocated

lens are rendered much safer when procaine-hyaluronidase is given by retrobulbar injection about five minutes before operation is started. A great deal of the hazard in these cases can be eliminated. The same is true with cataract extraction with increased intraocular pressure. With an eye, under pressure, the hypotony induced with at least 25 to 30 units hyaluronidase in three cc. procaine-epinephrine solution will obviate the possibility of loss of contents during the course of the operation.

5. In cases of glaucoma, when it is desired to obtain at least a temporary reduction of the intraocular pressure, this can be accomplished by a retrobulbar injection of about three cc. of procaine and epinephrine containing 30 t.r.u. of hyaluronidase (Wydase).

6. The diffusing property of hyaluronidase was also found to be beneficial in post-operative edema and chemosis following cataract operations and enucleations. With orbital and intraocular hemorrhage resulting from trauma, a retrobulbar injection of 150 t.r.u. in three cc. of procaine-epinephrine solution was followed by rapid recession and absorption of the hemorrhage. In cases of retinal edema resulting from trauma, a retrobulbar injection containing 50 t.r.u. administered early is followed by rapid diffusion and disappearance of the edema.

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COPPER WITHIN THE EYE 30 YEARS SIMULATING TUMOR

REPORT OF A CASE

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The occurrence of copper within the eye has provoked considerable discussion in the literature regarding toxicity and eventual prognosis for the eye since the early experiments of Leber.

The following case report is of unusual interest for two reasons: (1) Copper was known to have been within the eye for 30 years without evidence of chalcosis; (2) following this long period of quiescence, it simulated an expanding intraocular tumor by the process of fibrous encapsulation, cellular infiltration, and adjacent hemorrhage.

It appears to be reasonably certain at present that the intense inflammatory reaction with subsequent loss of the eye is due to "pure" copper within the eye. When the intraocular particle is copper alloy in the usual ratio of 85 parts copper to 15 parts alloy, the reaction is much less severe and chalcosis may or may not develop. The ordinary percussion cap in commercial use contains approximately 85-percent copper, 10-percent tin, and five-percent zinc.

Stated in other terms, the inflammatory reaction of the eye seems largely dependent on the amount of ionizable copper and the size and location of the particle.

Severe ocular inflammation, such as one frequently observes following the retention of pure copper within the eye, was relatively uncommon in World War I, but copper cataract was often observed. This fact has been explained as the result of the substitution of alloys for pure copper when the latter metal became scarce (Jess³).

Severe reactions following retention of even purer forms of copper are not always immediate in onset. In a case seen by one of us (R. D. H.) a nine-mm. strand of copper wire within the eye for three months was removed from the vitreous with retention of

6/10 vision. A traumatic, paracentral lens opacity remained but no evidence of chalcosis could be observed.

FATE OF INTRAOCULAR COPPER

Copper within the eye may undergo absorption with deposition of copper particles, spontaneous expulsion, or encapsulation. Absorption with deposition of copper particles principally about the anterior surface of the lens and the posterior portion of the cornea is typical of ocular chalcosis.

It is known that an electrochemical current exists in the eyeball and that the current flows from the negative posterior pole of the eye to the cornea which acts as the positive pole. The explanation for the peculiar pattern of the copper distribution is based upon the resistance of certain structures (lens capsule and Descemet's membrane) to the migration of copper ions set into motion by the electric current normally flowing from the retina to the cornea.

The disc of the sunflower cataract appears to be influenced by the size of the pupil. Following dissolution or removal of the copper, regression of copper deposits has been noted (Bellows,² Rosen³).

Spontaneous expulsion of intraocular copper has been reported more frequently than any other foreign body (Cordes and Harrington⁴). This has been explained by the action of copper salts on the uveal tract and sclera which softens the tissues to the point of extrusion of the foreign substance.

There have been several reports of small particles of copper becoming encapsulated in the vitreous with retention of normal vision. A rare case of this description was reported by Decker.⁵

The following case illustrates encapsulation of the copper alloy (assumed to be 85-

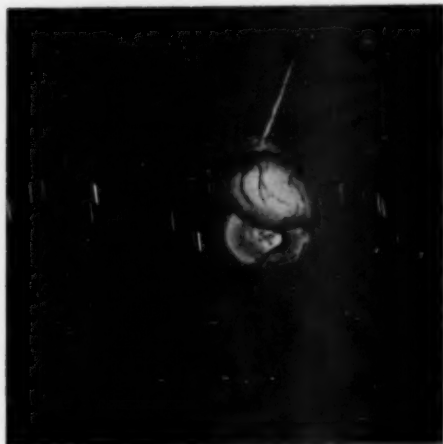


Fig. 1 (Mishler and Harley). Fundus drawing illustrating the greenish-gray mass extending five to six diopters above the disc. The scarred area behind the mass represents the site of the original trauma.

percent copper) with no demonstrable evidence of chalcosis after 30 years' retention.

CASE REPORT

History. The patient, a white man, aged 64 years, was first seen in the office (J.E.M.) on November 4, 1948, for a routine refraction of the left eye. He stated that the right eye had been sightless since an explosion of a percussion cap in 1920 which struck him above the right eyebrow. He did not become unconscious, but the wound above the eye bled freely. He recalled that he was treated by his family physician and that the right eye seemed unaffected at the time.

One week after the accident, however, the vision of the right eye was suddenly lost. This incident apparently caused little concern to the patient or the family doctor, because he never consulted an eye physician. The records of his family physician were not available. He remained in good health, and except for blindness of the right eye he denied any other ocular symptoms.

Examination of the eyes was recorded as follows:

The visual acuity was: O.D., nil; O.S., 6/7+ with correction. A thin, linear, healed scar, one cm. long, was situated in the midportion of the right eyebrow. The lids were normal.

The right pupil measured six mm. and the left, three mm. The right pupil failed to react to direct light, but the consensual reflex was intact. The right eye was divergent 25 degrees, but the ocular motility was adequate in all directions of gaze.

Biomicroscopy disclosed no scars in the cornea

or sclera, and the anterior segment appeared normal except for one area of pigment clumping on the anterior iris surface. Intraocular pressure was 23 mm. Hg (Schiotz).

The fundus of the right eye exhibited clear media and the retinal arterioles were generally constricted. There were a few discrete grayish-white spots in the macular region. The nervehead was white with marked loss of substance, and the margins were not clearly defined.

An elongated, narrow, white scar extended from the disc at the 12-o'clock position superiorly in the retina for three disc diameters towards the 2-o'clock position. Beginning at the disc margin and for a distance of one third of a disc diameter the scar tissue was elevated one diopter.

External examination, biomicroscopic, and tangent-screen field studies were normal for the left eye. Mild pigmentary changes of the senile type were noted in the macular area.

X-ray report. (Right eye)—"There is a minute irregular shadow of calcific density in the posterior portion of the eye measuring not more than one mm. in diameter. This may represent calcification within the eye, but the possibility of an artefact cannot be definitely ruled out."

The patient was not seen again until July 11, 1949, eight months later, when he returned complaining of a dull pain over the right eye. Fundus examination showed a circular grayish-green mass about one-half disc diameter in size and elevated three diopters.

The mass had a smooth surface with fine blood vessels coursing over the edge of the tumor. It appeared to be attached to the scarred area at the superior pole of the disc and moved slightly on tilting the patient's head. The intraocular pressure was 23 mm. Hg (Schiotz).

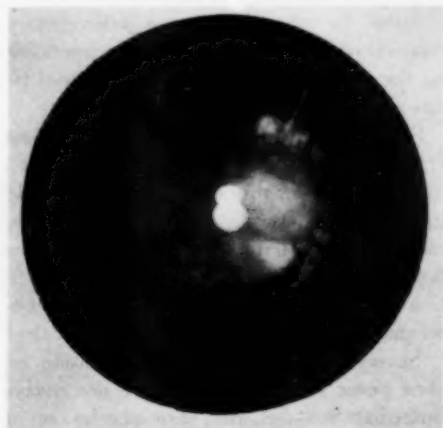


Fig. 2 (Mishler and Harley). Fundus photograph taken at the time of the drawing. The secondary optic atrophy and chorioretinal scarring can be seen in the background.

The patient was seen again on July 18, 1949, and it was apparent that the mass was now elevated four diopters. The intraocular pressure continued to be normal. A fundus drawing was made at this time.

Examination on July 25, 1949, showed that the mass now obscured the upper half of the disc and protruded forward five to six diopters. The surface blood vessels became more prominent. The mass appeared to have a darker-gray color than we had noted previously.

The patient was seen in several eye clinics and the diagnoses in order of preference were: (1) Malignant melanoma; (2) encapsulated foreign body; (3) cyst. Since the eye was blind and there was a possibility of malignancy, the eye was enucleated on August 1, 1949.

Pathology report. (Gross)—Adjacent to and partly overlapping the nervehead is an opaque mass measuring 2.5 mm. in diameter. Embedded in the mass is a nonmagnetic foreign body measuring one mm. in its greatest diameter.

(Microscopic)—The scar of entrance of the foreign body is not identified in the sections examined. There are red blood cells in the canal of Schlemm. There is a prominent pigment cluster on the anterior surface of the iris. The ciliary processes are hyalinized and their epithelium shows deep pigmentation and moderate proliferation. There are de-



Fig. 3 (Mishler and Harley). The encapsulated mass in a chorioretinal scar containing remnants of the nonmagnetic foreign body which dropped out upon sectioning. A small portion of the sclera and choroid can be seen to the left of the mass ($\times 20$).



Fig. 4 (Mishler and Harley). Section through the posterior wall of the encapsulated mass showing foreign-body particles in the dense fibrous tissue which has been infiltrated by lymphocytes and plasma cells ($\times 200$).

generative changes in the ganglion-cell layer of the retina and extensive peripheral cystoid degeneration is present.

Gliosis and perivascular lymphocytic infiltration are seen in the nervehead. There is also fibrosis present and the small portion of optic nerve appears atrophic.

The foreign body is in a chorioretinal scar which is encapsulated by dense fibrous tissue, the outer layer of which is infiltrated by lymphocytes and plasma cells. Adjacent to the scar is a suprachoroidal hemorrhage.

Diagnosis. Encapsulated intraocular foreign body in a chorioretinal scar, focal choroiditis, and recent suprachoroidal hemorrhage.

DISCUSSION

It seems probable that chalcosis lenticis failed to develop in this case since the copper particle was walled off by the inflammatory response of the choroid and retina. The usual electrochemical reaction failed to take place, and the lens was spared the formation of the typical sunflower cataract.

The increase in the extent of the mass was apparently induced by the adjacent hemorrhages and cellular infiltration. The greenish discoloration noted on the surface of the mass

was probably due to copper salts and gave a clue to the diagnosis.

It is of interest to speculate on the cause for the sudden loss of vision in the right eye one week following the accident. The foreign body must have landed in the region of the superior portion of the optic nervehead, judging by the appearance of the chorioretinal scar. Direct trauma and/or hemorrhage were probably primarily responsible for the optic atrophy. Expulsion of the foreign body from the disc margin with subsequent encapsulation would seem to be the logical sequence of events.

Franklin and Cordes⁶ reported a case which demonstrated the remarkable tolerance of copper within the eye for 46 years. In their case the eye became blind following the accident and remained quiescent until the late development of anterior uveitis and secondary glaucoma with sympathetic irritation of the eye. Sectioning of the eye following enucleation showed that the posterior half of the eyeball had been converted into a bony cup in which true ossification could be demonstrated.

These authors reviewed the literature and commented upon a number of cases in which a retained foreign body had remained intraocular and quiescent for many years. The

longest period of tolerance was recorded for a fragment of stone which lay dormant in the iris 54 years.

The different structures of the eye may show a variation in the tolerance of foreign bodies. It has been noted that the lens and anterior chamber often show a fair tolerance for small foreign particles. Foreign bodies in the iris and the vitreous usually precipitate a marked inflammation, and it is exceptional when they are well tolerated. The ocular reaction also differs markedly in its response to various classes of foreign substances. Lead, aluminum, wood, glass, and stone generally cause little reaction, whereas iron and copper often provoke extensive inflammation.

SUMMARY

1. A case is presented which was unusual in that copper was known to have been within the eye for 30 years without evidence of chalcosis.

2. During the final eight months' period of observation it simulated an expanding intraocular tumor.

3. The fate of intraocular copper and the tolerance of foreign bodies are briefly mentioned.

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AN EXPLANATION OF THE CORNEAL HAZE AND HALOS PRODUCED BY CONTACT LENSES*

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The inability of individuals to wear contact lenses for prolonged periods is caused primarily by a deterioration of the optical system as a result of corneal haze and halos. These conditions have been variously ascribed to alterations in metabolism of the cornea, interference with the perilimbal circulation, and use of fluids underneath the contact lens which are not of the proper tonicity or hydrogen-ion concentration. No evidence that any or all of these explanations can adequately account for the corneal clouding has been presented.

The present investigation was designed to determine the mechanism by which corneal clouding takes place with the hope that such knowledge might make it possible to delay or eliminate the appearance of corneal haze and halos when contact lenses are worn.

The choice of experiments was based on the observation of Cogan and Kinsey¹ that normal corneal transparency is dependent upon the maintenance of the cornea in a partial state of deturgescence.

This concept is derived from studies² in which it was shown that the surface membranes of the cornea (epithelium and endothelium) are permeable to water but not to salts, hence are semipermeable, and envisages that under normal conditions there is a continuous passage of water from the limbal regions of the cornea toward its center and out into the tears anteriorly and into the aqueous humor posteriorly.

This transfer of water is believed to take

place as a result of differences in the concentration of dissolved materials in the stroma of the cornea, and in the tears and aqueous humor, the latter fluids being hypertonic to the cornea. The imbibitory forces of the corneal micellae, however, tend to oppose the osmotic forces and the balance between these forces determines the degree of corneal hydration. Normally the balance is such that the corneal stroma is maintained in a state of relative deturgescence as shown by the observation that the cornea devoid of surface membranes will swell whenever it is placed in any aqueous solution irrespective of tonicity.³

The state of deturgescence seems to be associated with corneal transparency, as already indicated, since after an increase in hydration, as for example that which occurs following damage to the epithelium or endothelium or after reversal in the osmotic pressure relation between the inside and outside of the cornea, the cornea becomes cloudy and eventually opaque.

The appearance of corneal haze and halos might, therefore, be expected to indicate that some change in hydration of the cornea has taken place. Assuming that initially the osmotic relation between the cornea and the fluid used beneath the contact lens is approximately the same as that which exists normally between the cornea and tears, that is, that the solution is hypertonic to the corneal stroma, water would be expected to move from the cornea into the solution.

This movement of water would result in progressive dilution of the contact lens solution, a process which would occur until the solutions within and without the cornea become isotonic. Under these conditions, unlike in the normal eye where the dilution effect is compensated by renewal of tears and by evaporation, the imbibitory forces of the

* This work was performed in the Howe Laboratory of Ophthalmology, Harvard Medical School, and was part of a joint study with Dr. George Smelser, Department of Ophthalmology, Columbia University, College of Physicians and Surgeons, on the basic physiology of the cornea as it is affected by use of contact lenses. The project was supported by a grant from the office of the Surgeon General, Department of the Army.

† Kresge Eye Institute.

TABLE 1
COMPOSITION OF THE SOLUTION AND TONICITY

Composition	Millimolar
KH ₂ PO ₄	5
NaHPO ₄	5
Glucose.....	10
NaHCO ₃	230
Methyl cellulose 1%.....	—
Total*.....	250

(pH 7.2)

Osmotic pressure... 228 millimolar equivalent NaCl

* The activity coefficient of NaHCO₃ compared with NaCl was observed in other experiments⁶ to be 0.9. This accounts for the difference between the apparent theoretical and determined values for tonicity.

cornea would be unopposed and the cornea would begin to pick up water.

EXPERIMENTAL

The first series of experiments was designed to determine whether the tonicity of a fluid used beneath the contact lens changes significantly with time of wear and, if so, to ascertain the rate of such change. The second series of experiments was designed to determine whether the cornea becomes hydrated.

METHODS AND MATERIALS

The osmotic pressure of solutions was measured by the thermo-electric method of Baldes;⁴ the procedure requires only one or two microliters of solution for a determina-

tion. Repeated measurements with known solutions indicated that the method was accurate to 0.5 milliequivalents of sodium chloride per liter. Corneal thickness was measured by an optical method devised by Donaldson⁷ and Cogan.⁸

A special contact-lens solution was prepared[†] having approximately the same tonicity as that estimated for the film of tears overlying the cornea, that is, a tonicity equivalent to a sodium-chloride solution of 1.3 percent. The composition of the solution and tonicity, as determined experimentally, are shown in Table 1.

Standard contact lenses and Dallos lenses were employed in this investigation. These lenses were worn by volunteer subjects whose eyes were normal and who were accustomed to wearing such lenses. (All the subjects reported that the special solution used with

* Dr. David Donaldson performed the measurements of corneal thickness.

† Contact-lens solutions which were available commercially were not employed in this study because measurement of the osmotic pressure of the only two brands tested indicated the tonicity of both these solutions to be 153 milliequivalents of sodium chloride per liter, a value corresponding to a sodium-chloride solution of only 0.88 percent. Since these solutions were approximately isotonic with blood, and therefore presumably essentially isotonic with the cornea, it would not be expected that any appreciable dilution would occur during use with contact lenses and, in any case, on the basis of the theory outlined above, no further experiment would be required to account for increased corneal hydration with the use of such hypotonic solutions.

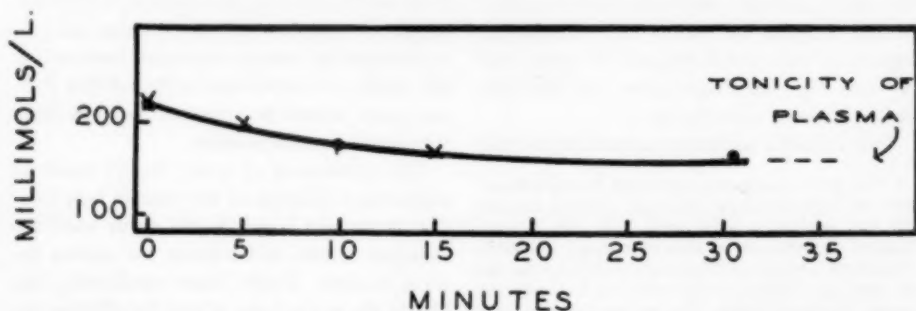


Fig. 1 (Kinsey). Change in tonicity of the solution used beneath the standard contact lens with time of wear (one subject).

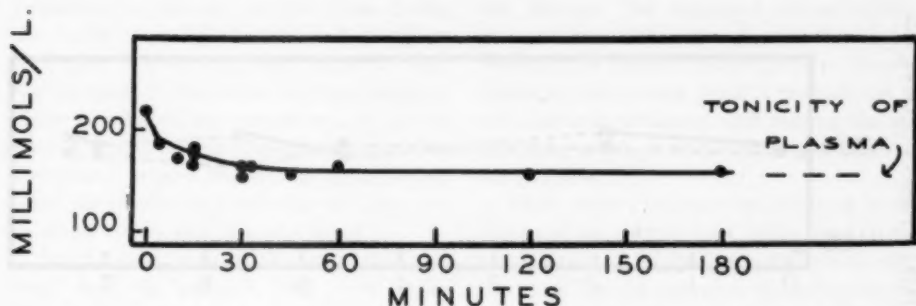


Fig. 2 (Kinsey). Change in tonicity of the solution used beneath the standard contact lens with time of wear (composite, seven subjects).

the lenses was comfortable.) Fluid for measurement of osmotic pressure was obtained after various periods by removal of the lens while the head was maintained in a downward position. In the case of the standard lens sufficient fluid was readily obtainable. In the case of the Dallos lens, however, only a film of fluid remained on the lens so that only measurements of corneal thickness could be obtained.

RESULTS

The osmotic pressure of the fluid removed from the standard contact lens after 5, 10, 15, or 30 minutes of wear, along with that of the original lens solution, is shown in Figure 1. The crosses represent repeated measurements on the right and left eye on one day, and the solid circles, the right and left eye on the subsequent day.

A composite curve representing similar measurements on samples removed from contact lenses after longer periods of wear (seven subjects) is shown in Figure 2. In all instances the tonicity of the contact lens solution decreased rapidly. Within less than 30 minutes the tonicity of the fluid corresponded to that of blood plasma, and presumably, therefore, to that of the fluid within the cornea.

The thickness of the cornea was measured in one subject before and after a contact lens was worn for 15 minutes in one eye and 30 minutes in the other eye (fig. 3),

and for one and three hours in the two eyes of another subject (fig. 4).

Corneal thickness did not change significantly in the first subject but increased in the second subject. The change in thickness was accompanied by corneal haze. The tonicity of the fluid beneath the lens was also determined and observed to decrease rapidly, as was noted in previous subjects.

Results obtained when a contact lens was

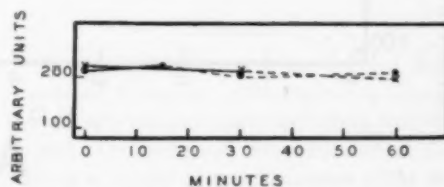


Fig. 3 (Kinsey). Change in corneal thickness as a result of use of a standard contact lens. The solid line represents the period during which the lens was worn. The broken line represents the period after removal of the lens.

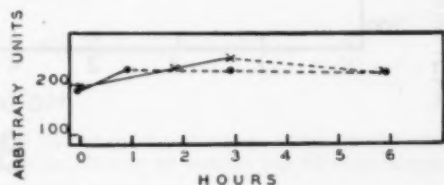


Fig. 4 (Kinsey). Change in corneal thickness as a result of use of a standard contact lens. The solid line represents the period during which the lens was worn. The broken line represents the period after removal of the lens.

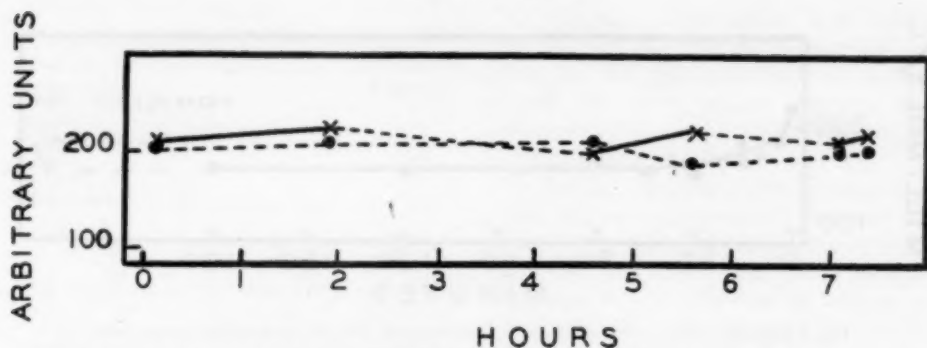


Fig. 5 (Kinsey). Corneal thickness following repeated insertion of a standard contact lens. The solid line represents the period during which the lens was worn. The broken line represents the period after removal of the lens.

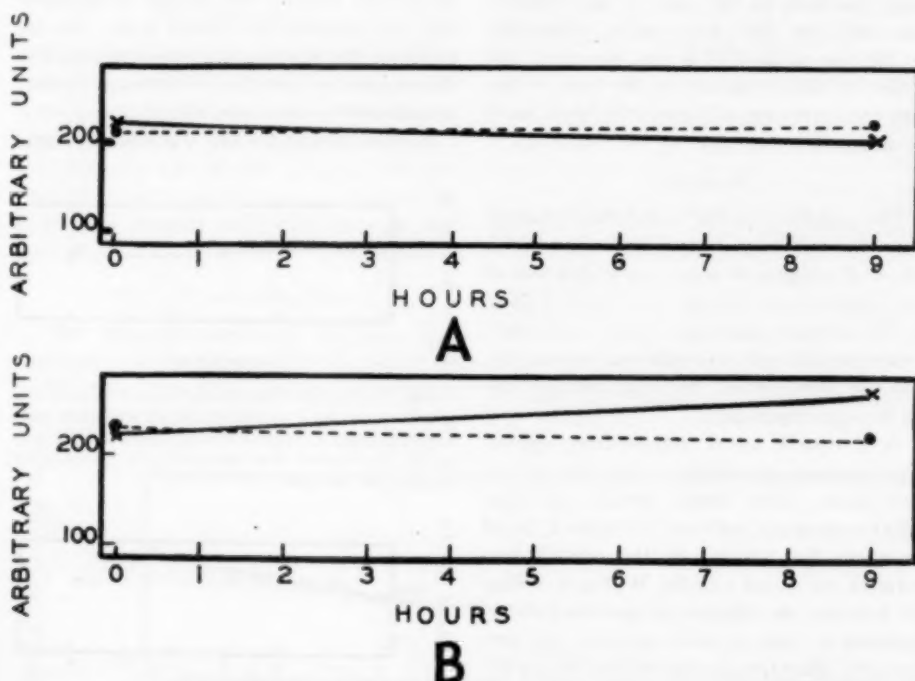


Fig. 6 (Kinsey). Change in corneal thickness as a result of use of a Dallos contact lens. The solid line represents the period during which the contact lens was worn. The broken line represents a control eye in which no contact lens was worn. (A) Illustrates results obtained with a subject in which no haze was experienced. (B) Represents results obtained in a patient who experienced haze.

reinserted in one eye several times during the course of an eight-hour period are shown in Figure 5. Following each period of wear the thickness of the cornea increased slightly. After removal of the contact lens, the cornea tended to return to its original thickness. The continuous broken line of the figure represents the results obtained with the other eye in which no contact lens was worn.

Similar measurements of corneal thickness were made on subjects who wore Dallos contact lenses, where considerably longer wearing times are possible. No increase in thickness of the cornea was noted in a subject who wore a Dallos lens for nine hours (fig. 6-A) and no corneal haze was experienced. The cornea increased in thickness, however, in a second subject who also wore a Dallos lens for nine hours (fig. 6-B). This subject experienced corneal haze.

DISCUSSION

The results of the present study suggest that the mechanism of corneal clouding produced by use of contact lenses is as follows. The hypertonic fluid employed for insertion of the lens, although initially capable of maintaining the osmotic gradient between the inside and outside of the cornea and thereby maintaining the cornea in a deturgescenced state becomes diluted with water from the cornea, so that after 20 to 30 minutes the fluid is essentially isotonic with blood plasma, and presumably also with the fluid within the cornea.

The imbibitory forces of the hydrophilic corneal substance are now no longer balanced by osmotic forces so that the cornea begins to take up water, thickening during

the process. The increased corneal hydration produces differences in refractive index resulting in optical inhomogeneity, thereby changing the cornea from a transparent to a translucent structure, and causing the appearance which is commonly referred to as corneal haze.

These studies indicate that alteration in the design of the contact lens, rather than in the composition of the fluid, would seem to offer the most fruitful approach to increasing the length of time of comfortable wear. The design of the lens should be such as to facilitate evaporation of the pericorneal fluid and to increase its rate of exchange with tears.

The increased length of wear reported for both the Dallos lens and the corneal contact lens appears to be ascribable to improvements of this type. Theoretically, it would seem that a material which would permit the free passage of water and thereby permit a more nearly normal rate of evaporation would be most suitable for a contact lens, providing, of course, it had the necessary optical and physical properties.

SUMMARY

Experimental evidence that corneal haze produced by use of contact lenses is caused by an increase in corneal hydration was obtained. The increased water content of the cornea is caused by the elimination of the osmotic gradient which normally exists between the fluids within and without the cornea which permits an increased amount of water to be absorbed by the hydrophilic corneal tissue.

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THE NEUROVASCULAR MECHANISM CONTROLLING OCULAR TENSION IN CONGENITAL GLAUCOMA OF RABBITS*

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The underlying causes responsible for congenital glaucoma remain unknown. Any investigation of the mechanism involved in this type of lesion would undoubtedly shed more light on the fundamental nature of glaucoma itself. It has been generally accepted that ocular hypertension in congenital glaucoma is brought about by structural abnormalities in the eye.

The changes most commonly associated with the disease are believed to be located in the region of the angle of the anterior chamber. Obstruction to the drainage of intraocular fluids takes place. Intraocular pressure becomes elevated and, because of the elasticity of ocular structures early in life, the globe becomes increased in size. A picture of buphthalmos familiar to the ophthalmologist is thus produced.

That congenital abnormalities in the structures of the eye do occur has been demonstrated by many, including Parsons,¹ Reis,² Meisner,³ and Byers.⁴ On the other hand, it has been found by Barkan,⁵ Callahan,⁶ and by others, that long-continued hypertension can obliterate the canal of Schlemm. Weekers and Weekers⁷ do not accept the prevailing view of a local mechanical obstruction to the angle, but believe that the neurovascular mechanism is involved.

Despite the fact that certain congenital deformities may be found in the eye, the mechanism which gives rise to glaucoma is by no means clear. This investigation was undertaken to evaluate the role of the neurovascular mechanism in cases of congenital glaucoma in adult rabbits and in their descendants.

NEUROVASCULAR MECHANISM IN BUPHTHALMOS (CONGENITAL GLAUCOMA)

Six chinchilla rabbits varying in age from one to three years were examined with the corneal microscope, slitlamp, and ophthalmoscope. These animals were obtained from several sources through advertising in trade journals. Many animals were submitted but only six were found to have buphthalmos.

The globes were large and protuberant. The conjunctivas were thickened, especially between the eyeball and the upper lid. A conjunctival pannus glaucomatosus covered parts of the cornea. There was cloudiness of the corneas, especially in the center, and the corneal diameter was increased from a normal of 11 to 13 mm. to 16 to 18 mm.

In some animals the cornea showed Fuchs's "aufhellungsstreifen." The anterior chambers were very deep. Crossing the surface of the iris were large blood vessels which are frequently found in human absolute glaucoma.

Whenever the fundus was visible, pronounced changes were found. The papillae were pale. There was peripapillary atrophy. The medullated fibers were atrophic or entirely missing. These findings characterized the picture of buphthalmos.

These animals were interbred and litters were obtained. Most of these animals died within the first few weeks. Two of the descendants lived long enough to allow satisfactory investigations. These animals were submitted to experiments at the age of nine months.

Four of the six buphthalmic rabbits were kept in a completely dark room for 15 hours. Whereas, in man the intraocular pressure is increased in the dark, it is lowered in the normal rabbit. At the end of 15 hours the

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TABLE 1

ROLE OF THE NEUROVASCULAR MECHANISM IN THE CONTROL OF INTRAOCULAR PRESSURE IN CONGENITAL GLAUCOMA OF RABBITS

(Four rabbits with congenital glaucoma were exposed to darkness for 15 hours. The animals were killed. Spinal fluid and pituitary glands were removed from the four rabbits. The pituitary bodies were separated into anterior and posterior lobes and each was suspended in saline. Spinal fluid, anterior and posterior pituitary suspensions were injected into test rabbits and intraocular pressures recorded.)

Results of Injections of Spinal Fluid into Test Animals		Results of Injections of Posterior Pituitary		Results of Injections of Anterior Pituitary	
Before	After Injection (mm. Hg Schiøtz)	Before	After Injection (mm. Hg Schiøtz)	Before	After Injection (mm. Hg Schiøtz)
24	36	22	28	26	29
24	36	20	25	25	26
25	28	26	31	25	30
23	26	25	27	23	29
22	21	24	23	26	29
21	20	22	22	25	28
25	25	25	24	24	28
28	25	25	24	24	28

INTERPRETATION: Injection of spinal fluid or posterior pituitary from normal animals exposed to darkness produces in test animals a significant decrease of intraocular pressure. Suspension of anterior lobe of normal animals causes an increase. On the other hand, spinal fluid and posterior pituitary from glaucomatous animals exposed to darkness produced either no change or an increase in pressure. These findings suggest a disturbance in the secretion of pituitary principles and an increase in the quantity of hyperpiesin in congenital glaucoma of rabbits.

animals were killed with air and the spinal fluid and the pituitary bodies were removed. The pituitary bodies were separated into anterior and posterior lobes and triturated in normal saline solution. Injections of the total suspension were made subcutaneously.

Test rabbits were injected intravenously with 0.5 to 1.0 cc. of spinal fluid obtained from the animals with buphthalmos. That much spinal fluid could be obtained from each one of the animals. It was demonstrated in a former report that spinal fluid contains pituitary principles which act on intraocular pressure.⁸

Several recordings of ocular tension were made in the test animals prior to injection and at 10-minute intervals for one to two hours after it. Tension was determined by the Schiøtz tonometer. The recorded readings were in terms of the third corrected curve of Schiøtz. The eyes were anesthetized with one drop of one-percent butyn. Tension was obtained with a 5.5 gm. and a 10 gm. weight.

A tension of 3.0 or more mm. Hg under

conditions as outlined was considered significant of a change due to experimental procedure as determined by our previous investigations. One test rabbit showed an increase in tension of 12 mm. Hg in both eyes. The second test animal had an increase of 3.0 mm. in both eyes. The remaining two test rabbits showed no change or a decrease of tension of 1.0 mm. Hg which was without experimental significance (table 1).

In our previous investigations we observed that spinal fluid from rabbits exposed to dark reduced ocular tension in most test rabbits by 2.0 to 5.0 mm. Hg.⁸ These results suggest the presence of an abnormal secretory activity of the pituitary principles with a predilection to an increase in the quantity of hyperpiesin, the pituitary substance which gives an increase in pressure.

Another group of test rabbits was injected subcutaneously with a one-cc. suspension in normal saline of the posterior pituitary removed from the animals with buphthalmos. The intraocular pressure was increased significantly in two test rabbits and decreased

without experimental significance by 1.0 to 2.0 mm. Hg in the other two animals (table 1). Posterior pituitary suspension from normal animals exposed to dark produced invariably a decrease in pressure.⁸

Injection of suspension of anterior pituitary body into test animals resulted in an increase of pressure of 1.0 to 6.0 mm. Hg (table 1). Anterior-pituitary suspensions from normal animals exposed to dark resulted in a rise of pressure of 3.0 to 10 mm. Hg.⁸ The experiments with crude suspensions of pituitary tissue give further indication that rabbits with congenital glaucoma have a disturbance of pituitary secretion with a resultant increase in the quantity of hyperpiesin.

Two of the remaining rabbits with buphthalmos were exposed to bright light for five hours. The animals were killed with air. Spinal fluid was withdrawn and injected intravenously in one-cc. volumes into test rabbits. Ocular tension was obtained several times prior to and at 10-minute intervals for two hours after injection. There was a consistent rise of ocular tension which varied from 5.0 to 8.0 mm. Hg (table 2). Spinal fluid taken from normal rabbits exposed to

strong light and injected into test animals gave a corresponding increase in test animals.⁸ Apparently, whatever abnormality exists in relation to pituitary secretion, there is no interference with the production of hyperpiesin.

NEUROVASCULAR MECHANISM IN DESCENDANTS OF RABBITS WITH CONGENITAL GLAUCOMA

Of the several litters resulting from interbreeding of rabbits with congenital glaucoma, all but two animals died before they were old enough to be subjected to experiments. The two remaining animals were examined with the corneal microscope, slitlamp, and ophthalmoscope. No abnormal changes were detected.

The animals were exposed to bright light for a period of five hours. Tensions taken before and after exposure did not reveal any significant variations. The animals were exposed to total darkness for a period of 15 hours. Ocular tension taken after that period did not reveal any significant changes (table 3).

These findings constituted an abnormal response. Normal animals subjected to light and dark responded by significant increases and decreases of intraocular pressure.

The two rabbits were subjected to the odor of left-citronellol. There were no changes in pressures taken prior to and after exposure to the chemical (table 3). Normal rabbits in other experiments responded by a significant increase.⁹ It was indicated in previous publications that responses to light, dark, and to odors are under the control of the neurovascular mechanism.⁸⁻¹⁰ On the basis of these findings, it may be deduced that, although the animals were free from signs of glaucoma, yet the diencephalic centers of the neurovascular mechanism were abnormal in the control of intraocular pressure.

The two rabbits were injected intravenously first with hyperpiesin (pituitary prin-

TABLE 2

ROLE OF THE NEUROVASCULAR MECHANISM IN THE
CONTROL OF OCULAR TENSION IN CONGENITAL
GLAUCOMA OF RABBITS

(Two rabbits with congenital glaucoma were exposed to bright light for five hours. The animals were killed. Spinal fluid was removed and injected into test rabbits and intraocular pressures recorded.)

Before Injection (mm. Hg Schiøtz)	After Injection (mm. Hg Schiøtz)
24	31
24	32
23	28
22	27

INTERPRETATION: Spinal fluid obtained from normal animals exposed to strong light and injected into test animals produces an increase in ocular tension. Similar results were obtained with spinal fluid from glaucomatous animals. The disturbance in congenital glaucoma of rabbits affects apparently the secretion of pituitary principles in a manner which results in an increase of hyperpiesin.

ciple which raises ocular pressure) contained in one cc. of spinal fluid. There was no change in ocular pressure (table 3). Normal animals injected with hyperpiesin responded by an increased pressure up to 10 mm. Hg.

After several days, the two rabbits were injected intravenously with miopiesin. There was no significant change in the ocular pressure (table 3). On the other hand when normal rabbits were given miopiesin they responded by a decrease of pressure up to 8.0 mm. Hg.

These observations suggest that the descendants of animals with congenital glaucoma show an abnormality of diencephalic response to pituitary principles. Since the two animals did not have ocular hypertension, it is evident that other regulatory mechanisms outside of the neurovascular and pituitary principles are capable of maintaining a normal intraocular pressure.

The two rabbits were then given orally dis-

tilled water in 40 cc. quantities per kg. body weight. Tensions were taken prior to and at 10-minute intervals for two hours following the administration of water. The intraocular pressures of the two animals were increased by 9.0 to 14 mm. Hg (table 3). The pressures did not persist as long but were higher than in normal animals.

This experiment suggests the presence of an instability of intraocular pressure in response to stimuli. It is postulated that this instability is due to the lack of normal secretion of the two pituitary principles, hyperpiesin and miopiesin, which normally maintain the stability through the medium of the diencephalic centers. It is further postulated that the instability of the regulatory mechanism predisposes to abnormal responses and to the development of clinically demonstrable glaucoma.

The two rabbits descendant from animals with congenital glaucoma were exposed to

TABLE 3

THE NEUROVASCULAR MECHANISM IN RABBITS DESCENDANT FROM GLAUCOMATOUS ANIMALS BUT WITHOUT EVIDENCES OF GLAUCOMA

(Descendants of glaucomatous animals were exposed to light, darkness, odors, injected with pituitary principles, and given distilled water orally. Intraocular pressures were recorded.)

Animals Exposed to Light	Animals Exposed to Dark	Animals Exposed to Odor of Left-Citronellol		Animals Given Either Hyperpiesin or Miopiesin		Animals Given Distilled Water Orally		
		Before (mm. Hg Schiøtz)	After (mm. Hg Schiøtz)	Before Hyperpiesin (mm. Hg Schiøtz)	After Hyperpiesin (mm. Hg Schiøtz)	Before	After in 25 & 45 min. (mm. Hg Schiøtz)	
18	20	19	20	21	21	19	33	24
17	19	20	20	21	21	18	27	21
20	21	26	27	25	25	28	40	35
20	20	26	27	25	25	27	40	31
26	25			Miopiesin				
27	25			23	21			
26	25			18	18			
26	24			26	25			
				25	24			

INTERPRETATION: In normal animals, exposure to darkness or to odor of left-citronellol produces a change in intraocular pressure. Descendants of glaucomatous animals showed no change. These findings suggest that there is a failure in the secretory mechanism of pituitary principles which act upon ocular tension.

Injection of pituitary principles into the descendants of glaucomatous animals produced no response in intraocular pressure. This finding suggests that one part of the neurovascular mechanism, probably the diencephalic centers, are so affected that they do not respond to pituitary stimuli. The pronounced rise in pressure and its more rapid decline after oral distilled water suggests an instability of maintenance of intraocular pressure. The experiment also indicates that the aqueous-plasma barrier is not disturbed.

TABLE 4

SECRETION OF PITUITARY PRINCIPLES CONCERNED WITH INTRAOCULAR PRESSURE IN DESCENDANTS OF RABBITS AFFLICTED WITH CONGENITAL GLAUCOMA

(Two rabbits without obvious signs of glaucoma but who were descendants of glaucomatous animals were exposed to darkness for 15 hours and then killed. The spinal fluid and the pituitary glands were removed. The posterior and the anterior part of the pituitary were suspended in saline. Spinal fluid and the pituitary suspensions were injected into test animals and their intraocular pressures recorded.)

Before injection of spinal fluid (mm. Hg Schiøtz)	After	Before injection of posterior pituitary (mm. Hg Schiøtz)	After	Before injection of anterior pituitary (mm. Hg Schiøtz)	After
20	20	27	25	27	28
20	21	26	25	28	29
25	26	25	25	25	25
25	25	25	25	24	24

INTERPRETATION: Spinal fluid and posterior pituitary of normal animals exposed to darkness decreases intraocular pressure in test animals. Anterior pituitary produces an increase. No changes were found in test animals injected with spinal fluid and pituitary principles from descendants of glaucomatous animals. These findings suggest that pituitary function concerned with maintenance of intraocular pressure is profoundly disturbed in animals without apparent signs of glaucoma but who are descendant from glaucomatous animals.

dark for 15 hours and then killed. The spinal fluid and the pituitary bodies were removed. The anterior and posterior parts of the pituitary organ were triturated each in one cc. of normal salt solution. The spinal fluid was injected intravenously and the pituitary suspension subcutaneously into test rabbits.

No changes in intraocular pressure were obtained in any of the test rabbits (table 4). A similar exposure to dark of normal rabbits followed by injection of their spinal fluid and posterior pituitary into test rabbits induced a lowering of pressure. The anterior pituitary resulted in an increase.⁸

These experiments supply further evidence that the pituitary body in the descendants of rabbits with congenital glaucoma fails to elaborate pituitary principles which serve to regulate intraocular pressure by their action on the diencephalic centers.

SUMMARY AND DISCUSSION

Experiments on six rabbits with congenital glaucoma (synonyms: buphthalmia, hydrophthalmia¹¹) indicated a significant alteration in the normal function of the neurovascular mechanism which regulates intraocular pressure. Stability of pressure was found to be seriously disturbed. Since instability of ocular tension is as important as its height

in the development of glaucoma, the factors which contribute to it necessarily play a part in the cause of the disease. Congenital glaucoma in rabbits is associated with a faulty secretion of pituitary principles with an increased quantity of hyperpiesin.

The two descendants of the rabbits with congenital glaucoma gave significant findings. Although the two animals did not have signs of glaucoma, they showed evidences of dysfunction of the neurovascular mechanism. There was a lack of secretion of pituitary principles. The diencephalic centers failed to regulate properly the stability of the intraocular pressure.

Although no correlation has been established between primary and congenital glaucoma, the possibility must neither be overlooked nor disregarded. In view of the findings in the descendants of glaucomatous animals, consideration must be given to this possibility. The animals were without clinical signs of glaucoma and yet they showed fairly profound abnormalities of the neurovascular mechanism which is one of the controls of intraocular pressure.

Elwyn's¹² point of view that "primary glaucoma is the result of an inherited inherent defect in the central mechanism integrating and regulating the individual fac-

tors which maintain the tension within the eye at a normal value," finds suggestive corroboration in the results obtained in the descendants of glaucomatous animals.

The mechanism concerned in hereditary transmission of glaucoma is unknown. Most observers accept the concept that in congenital glaucoma the structure of the eye varies from normal. Malformations of the filtration angle, small eyes, and large lenses

have been implicated. These investigations indicate that an instability of intraocular pressure exists in animals without any of these stigmas. This instability is produced by abnormalities of secretion of pituitary principles and by impaired diencephalic centers concerned with the regulation of intraocular pressure.

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PLASMA IMPLANTATIONS IN THE CORNEA*

G. W. H. M. VAN ALPHEN, M.D.
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Up to the present time the problems of the fate of the corneal transplant, the conservation of its individuality or its partial and/or total absorption and substitution, have been studied by means of microscopic follow-ups of transplants.

These investigations were seriously handicapped by the fact that a great similarity existed in the microscopic picture between the host cornea and the graft. Furthermore, it is not known in which manner a total substitution occurs, if indeed it occurs at all. Investigations with artificially induced scars do

not sufficiently indicate the full regenerative potency of the cornea.

These difficulties are overcome on implanting a graft without a histologic structure, having the property of gradual absorption. In these circumstances it becomes possible to study the "pure" behavior of the host cornea, itself.

Blood plasma was chosen as the "graft." It has no histologic structure and, if placed in the anterior chamber of the eye, was shown to dissolve in about a fortnight. Biochemically, however, plasma shows a definite structure; this is of possible value in the results of the implantation.

The incorporation into tissue cultures of certain structures, such as threads of nylon or glass, and the influence of the highest tension in the underlying rubber-base much

* From the University Eye Clinic. I wish to thank Dr. P. van der Meer, Dr. J. A. Cohen, Dr. H. L. Booy, Prof. P. J. Gaillard, Dr. G. J. Verdonck, and Mr. W. A. Blokhuis for their unstinted help and valuable discussions, and Mr. L. Beumer for his help in laboratory technique.



Fig. 1 (van Alphen). Host cornea (to the left) and plasma graft four days after implantation. The graft is partially torn off. The proliferation of the host cornea's endothelium is continued over onto the graft (E-E). The epithelium has also proliferated, though rather less than the photograph would seem to indicate. In the graft, remains of the plasma are still clearly visible, particularly in the form of bars. Note the migrated cells.

improve the rate of cell migration (Weiss*). Since plasma has a fibrillar structure, a stimulating influence on cell migration may be expected.

PREPARATION OF PLASMA

Rabbit blood, obtained on puncture of the heart, is received into a tube over oxalate of sodium and centrifuged. The oxalated plasma is sucked up and precipitated at 37° C. with a quantity of CaCl_2 , such that the clotting-time passes a minimum. As this plasma contains calcium, another method was employed later on in which blood was centrifuged in ice-cooled paraffined tubes. Then the syneresis water is removed from the plasma clot by applying slight pressure. A good plasma film, nearly two mm. in thickness, is obtained in this way.

IMPLANTATION

The cornea of a rabbit was totally trephined (diameter 4.1 mm.) and a plasma film of the same diameter was inserted. The

first implantation was carried out following Castroviejo's method.[†]

From this experiment it became clear that the operation itself was feasible; since the anterior chamber was reformed and the graft did not dissolve too rapidly, the eye was preserved. Because the fixation sutures cut deeply into the soft plasma, however, all the next implantations were fixed by means of contact glasses.

Six plastic contact glasses of different sizes were manufactured to fit rabbits' eyes. Prior to each operation the best-fitting glass was selected.

The normal cornea was then trephined under atropine, and the plasma film was cut with the same trephine. The excised piece of plasma film was then inserted into the eye, a contact glass was placed upon it, and firm pressure was applied for one to two minutes. The plasma soon adhered to the borders of the cornea and, at the end of this time in most cases, the anterior chamber had reformed. Penicillin-atropine ointment was applied and the eyelid sutured.



Fig. 2 (van Alphen). High-power view of Figure 1. Proliferation of endothelium at the edge of the host cornea's Descemet's membrane.

* Weiss, P.: Arch. f. Entw. Mech., 116:438, 1929.

† I wish to thank Dr. C. Kok van Alphen for carrying out this first implantation, Dr. E. G. Wijngaarde for valuable assistance in the other experiments, and Mr. D. Laman for anesthesia.

SUBSEQUENT COURSE

At the end of three days, in most cases, no details were visible, as the dissolving plasma clouds the contact glass. After six to eight days, the contact glass is removed and the graft shows a chalk-white coloration. After 10 days the color of the graft has, more or less, the aspect of milky glass.

On the 12th to 16th day, small radial blood vessels appear, originating in the limbus in the direction of the graft and penetrating into the graft in only a few of the observed cases. These vessels disappear again in from four to eight days. Twelve to 24 days after operation, the borders of the graft start to become transparent, and this proceeds extremely slowly toward the center of the graft.

In all, 32 rabbits were operated upon. The results were:

Lost (panophthalmia)	4
Enucleation within 25 days of implantation	6
Thick macula corneas	10
Thin macula corneas	12

The transparency may be tabulated as follows:

Cleared up at the borders	10
Clear epithelium and but slight stroma cloudiness and cloudy Descemet's membrane	5
Clear epithelium and stroma; Descemet's membrane still cloudy	2
The same but with a very slight central clouding of Descemet's membrane ..	2
Absolutely transparent	0

In only five cases was the implanted plasma film obtained from the blood of the same rabbit on which it was later grafted. In all other cases, the plasma was derived from an arbitrarily chosen rabbit. In the



Fig. 3 (van Alphen). Enlarged part of the plasma graft of Figure 1. Migration of endothelial cells.

results, however, no difference was noticeable; a retarded dissolving of the plasma of auto-implants in the anterior chamber was suggested by the longer duration of cloudiness of the aqueous.

The microscopic sections of the 28 implantations show the manner in which the plasma is being "rebuilt" into normal cornea. This process and its variations will be summarized here.



Fig. 4 (van Alphen). Later phase of proliferation of the endothelium at the edge of the host's Descemet's membrane. Beginning of new Descemet formation (three to four weeks after implantation).

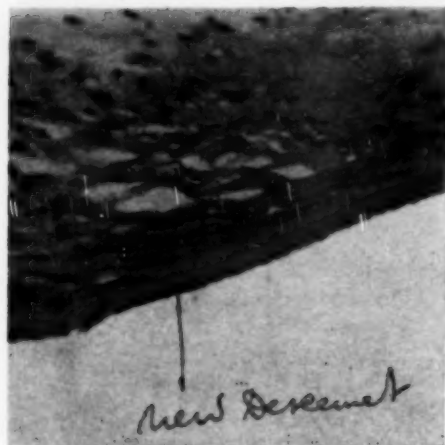


Fig. 5 (van Alphen). Beginning of new Descemet formation (three to four weeks after implantation).

The graft, four days after the implantation, is wholly filled with spindle-shaped cells, many of which show mitotic division. The indication of the origin of these cells is very clear indeed—endothelium of the host cornea at the edge of Descemet's membrane has proliferated enormously and these endothelium cells are migrating into the plasma graft. These migrated cells completely correspond in shape, size, and structure to the cells of the original endothelium. Nearly all micro-



Fig. 6 (van Alphen). Proliferation of the endothelium eight weeks after implantation. Note host's Descemet's membrane and newly formed Descemet's of the graft.

scopic sections of the plasma-implanted corneas still clearly show the original proliferation of the endothelium at the edges of the host's Descemet's membrane.

The host cornea's epithelium also is proliferating—though much less intensively than the endothelium—and these epithelial cells, four days after implantation, have already crossed over to the edges of the plasma graft. Numbers of these cells appear to come loose from the context of the epithelium, and to swarm into the plasma in a similar manner.

LATER COURSE

In the protoplasm of the spindle-shaped cells in the graft, after eight to 15 days, a distinct fibrillary structure appears, which is shown exclusively, at the beginning, in the Gömörry-stained specimens; and later also with the Weigert-Gieson staining method. In the same period many specimens also show the beginnings of lamellar formation and flattening of the cells.

In a later phase—about eight weeks after implantation—the newly formed stroma is hardly to be distinguished from the stroma of the host cornea in many cases. The lamellar structure, in about half the cases, shows slight to very distinct irregularities, due largely to inflammation which may be accompanied by ingrowing blood vessels.

In the initial phases of the chronic proliferative inflammation, a strong mesenchymal proliferation occurs, which shows exudate, leukocytes, accumulation of histiocytes, mast cells, and phagocytic giant cells. In later phases all this results in a very irregularly built fibrous tissue.

In the early phases the stroma of the host cornea is, in many cases, slightly infiltrated with leukocytes. The stroma cells situated in the near vicinity of the graft are considerably swollen, but no signs of mitosis were ever observed.

In half the number of cases, a newly formed intact endothelium was found and, moreover, a newly formed Descemet's mem-

brane was present in six of the cases. This new Descemet's membrane is thinner and stains more faintly than the host Descemet's membrane. Apart from these findings in three of the seven eyes enucleated early in the experiment (three to four weeks after implantation), Descemet's membrane was present in a rudimentary form.

In only four cases was the epithelium absent. All the other cases showed intact epitheliums, some of which were very regular, and others considerably irregular in appearance. In two cases, large bullae had formed. In one case, there was such a proliferation of the epithelium that it resembled a granuloma.*

Even three to four weeks after implantation, definite parts of the epithelium clearly indicated a gradual transition of epithelium cells into stroma cells. It is obvious that the epithelium takes its part in the building-up of the stroma, though to a much lesser extent than the endothelium.

The time of epithelization of the surface of the graft varies considerably—between 12 and 30 days—being determined by means of fluorescein staining in the living eye. In one of the microscopic sections a very regular intact epithelium was found as early as 14 days after implantation.

Bowman's membrane is absent in rabbits and it may be that its function is taken over by the basal membrane of the epithelium. In 10 cases the new epithelium showed a distinct basal membrane.

A summary of microscopic findings in 22 eyes enucleated after more than three weeks following implantation shows:

EPITHELIUM	
Absent	4
Present	18
Regular	11
Irregular	7
BASAL MEMBRANE	10

* In this case, in the newly formed stroma many cells resembling eosinophilic leukocytes were found, the significance of which remains obscure.

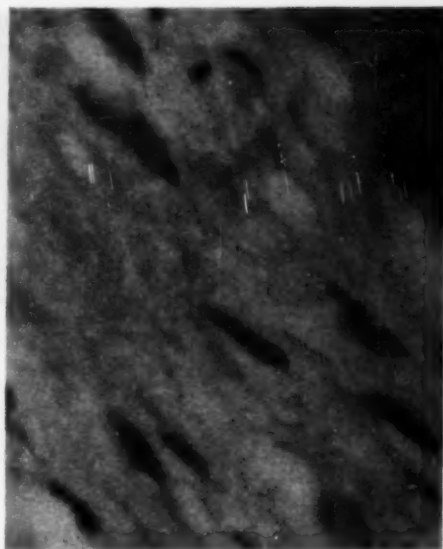


Fig. 7. (van Alphen). The newly formed stroma, 20 days after implantation. Migrating endothelial cells constitute a three-dimensional reticulum.

STROMA	
Regular	10
Irregular	12
Fibrous	5
Vascularization	5
DESCMET'S MEMBRANE	
Present	6
Indicated	3
ENDOTHELIUM INTACT	11
SYNECHIAS (anterior)	7

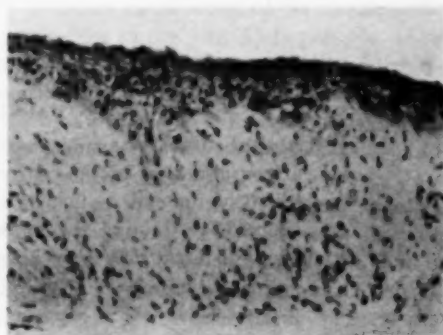


Fig. 8 (van Alphen). Gradual transition of epithelial cells of the graft into stroma cells (three to four weeks after implantation).

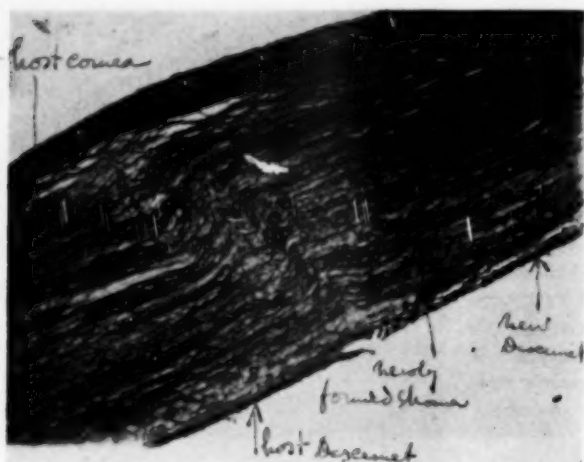


Fig. 9 (van Alphen). Host cornea and newly formed cornea three months after implantation. The place of transition is marked by a slight irregularity in the lamellar structure of the stroma. Also the host's Descemet's membrane is thicker and stains more deeply than the newly formed Descemet. Remains of proliferation of the endothelium.

CONCLUSIONS

From experimental work on rabbits it became clear that implantation of a plasma film into a wholly trephined normal cornea is possible; fixation being by means of a contact glass.

It was shown that the host cornea is able to build up into this plasma medium a new tissue which very closely resembles the normal cornea in histologic structure and transparency (a slight central clouding of Descemet's membrane excepted).

The host cornea's endothelium appears to be essentially significant in the formation of

stroma, Descemet's membrane, and the new endothelium.

The new epithelium is derived from the host cornea's epithelium, the proliferation of which may also be of some significance in the stroma formation, though its share seems to be rather slight.

These investigations appear to be of theoretical value only, in so far as they indicate the potency of the host cornea, the possibility of corneal regeneration in a proper medium, and the manner in which this regeneration takes place.

University Eye Clinic.

OPHTHALMIC MINIATURE

When the adhesion (symblepharon) begins at, is continuous with, and arises from that part of the conjunctiva which is reflected from the lid to the ball of the eye, so that on raising the eyelid a broad attachment is perceived, restraining the motions of the eye, it ought not to be meddled with for it may be increased, but it will never be diminished.

Guthrie, *Lecture on the Operative Surgery of the Eye*, 1830.

NOTES, CASES, INSTRUMENTS

A COMBINED BRIDLE AND CONJUNCTIVAL RETRACTION SUTURE*

JOHN THAYER SIMONTON, M.D.
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When employing the method of cataract surgery in which a sliding conjunctival flap is dissected upward from the limbus, I have found this new bridle suture of value.

METHOD

Following routine preparation of the eye for cataract surgery, a lid speculum or lid traction sutures are used to expose the eye. A peritomy is done from the 9-o'clock position up and around to the 3-o'clock position. The conjunctival flap is then freed up by further blunt and sharp dissection so that it may be easily drawn down over the upper one third of the cornea.

A Desmarres lid retractor is used to retract the flap (fig. 1), while the superior

rectus muscle is picked up with Lister forceps about five to seven mm. back of the insertion site. The bridle suture is then placed through the muscle. The Desmarres lid retractor is removed and a serrefine is attached to the five-inch reins of the bridle suture.

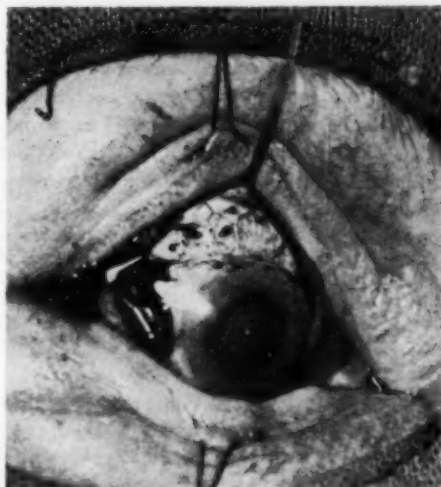


Fig. 2 (Simonton). The suture retracts the conjunctiva away from the limbus.

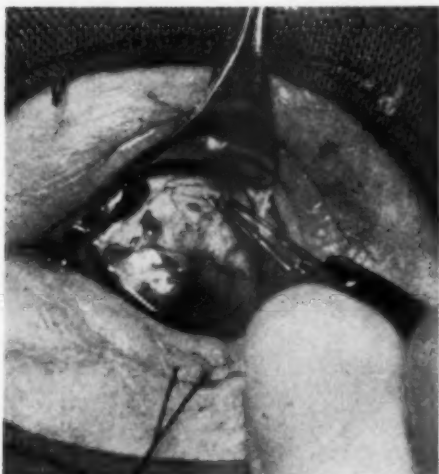


Fig. 1 (Simonton). Direct visualization of the muscle is possible.

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ADVANTAGES

1. Direct visualization of the muscle while placing the suture (fig. 1) is possible. Thus the suture can be placed well back of the insertion site of the superior rectus. The resultant effect of any pull on the bridle suture is a tendency for the corneoscleral wound to close rather than to gape.

2. As seen in Figure 2 the suture retracts the conjunctiva away from the limbus, thereby maintaining a clear field which is especially important when the section is made and when the corneoscleral sutures are placed.

3. Annoying subconjunctival hematoma is avoided.

4. Repeated attempts to place the bridge suture properly are avoided.

DISADVANTAGES

1. A few extra minutes are required to expose the superior rectus and place the suture through the muscle well back of the insertion site.

2. There is more surgical trauma to the eye.

SUMMARY

A new type of combined bridge and conjunctival retraction suture is presented for use in the method of cataract surgery in which a sliding conjunctival flap is employed. This suture has been used in 35 cases and found to be of value for the reasons enumerated.

Blind Brook Lodge.

SCLERECTOMY IN RETINAL DETACHMENT*

WITH NO ATTEMPT TO SEAL THE DISINSERTION: REPORT OF A CASE SUCCESSFULLY TREATED

FRANK A. VESEY, M.D.
New York

HISTORY OF THE CASE

At two o'clock in the morning of August 12, 1948, D. S. R., a Puerto Rican cafeteria worker, aged 40 years, was admitted to the hospital as an emergency case, with symptoms that seemed to indicate an attack of acute glaucoma.

On the same afternoon when I first examined this patient, the following history was obtained. Soon after he came out of the refrigerator room at the cafeteria where he was working, he had lifted the top from the coffee maker. Steam had enveloped his face and made him sneeze violently. After sneez-

ing, he suddenly lost vision and, a little later, developed a severe temporal headache.

Eye examination revealed vision to be: R.E., faint light perception; L.E., perception of hand movements. Externally the eyes were normal, as were the adnexa. No signs of inflammation were present in either eye. Both pupils were moderately narrow; there was no reaction to light from a flashlight, without magnification, in either eye.

Questioning brought out that he had been injured in his right eye when a boy, but he did not remember the course of the disease that followed.

Atropine and 10-percent neosynephrine were used to produce dilatation. The pupils dilated poorly but, after three quarters of an hour, a fairly wide dilatation was obtained in the left eye; some dilatation in the right eye.

The fundus of the right eye was not visible because the lens was completely opaque; the left eye showed the media to be fairly clear. The disc was visible, the borders well defined, and the vessels could be followed over the retina which was almost entirely detached.

An area with a border shaped like a parabola extended from the lower part of the disc to the periphery, from the seven to the five-o'clock positions. This area showed no retinal vessels. Its appearance was typical of disinsertion of the retina (fig. 1). A diagnosis of retinal detachment was made.

Since it seemed that a diathermy operation might not cure the condition, it was decided to do a sclerectomy.

After a complete laboratory work-up had disclosed that no inflammation was present, the patient was operated on August 19th under Van Lint-O'Brien anesthetics. Retrolbulbar novocaine and local pontocaine applications were used.

SURGICAL TECHNIQUE

The conjunctiva was divided by an incision parallel to the limbus and 10 mm. from it. The superior rectus was detached and, about

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10 mm. behind the tendon of the muscle, an oval-shaped sector of the sclera was excised, two-mm. wide and 20-mm. long. The choroid was cut through and about two or three cc. of fluid were drained from under the retina. The scleral wound was united with black silk sutures as the excision went along.

After the closure of the scleral wound three cc. of normal saline were injected into the vitreous cavity, and an approximately normal tension, or a little higher, was reached. The superior rectus was reattached by catgut sutures and the conjunctival wound was closed by a continuous black-silk suture.

After operation, the vision was tested and the patient counted fingers very easily at three feet. Atropine and sulfathiazole ointment were instilled and both eyes were dressed.

At the first dressing, seven days after the operation, the fundus was not visible at all and the patient had light perception only. This was supposed to be due to a rather large vitreous hemorrhage. The eye was quiet, however, and was again dressed with atropine and sulfathiazole. For the next few days, the patient complained of pain in and



Fig. 1 (Vesey). Almost complete funnel-shaped detachment of the retina, O.S. The large disinsertion, parabolic in shape, is outstanding.

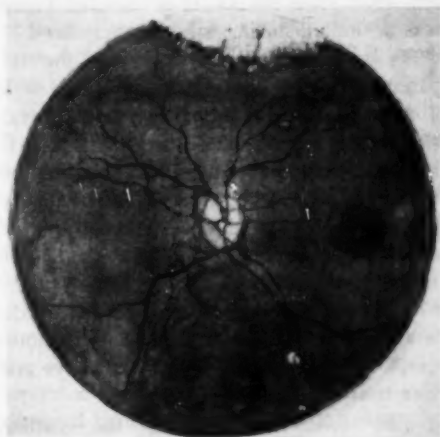


Fig. 2 (Vesey). The fundus appears fairly normal. The atrophic area above, which corresponds to the scar of the sclerectomy, and the two white patches along the lower temporal vein below should be noted. The sheathing and white patches are probably due to cramping of the vessel by the wrinkling of the detached retina. The characteristic faint borderline is discernible around the stippled area bounding the area of former disinsertion.

around the eye and a total of one million units of penicillin was given intramuscularly. The tension of the eye was normal to fingers. Otherwise, recovery was uneventful and the continuous suture was removed from the conjunctiva on the 14th day.

COURSE

The vitreous opacity started to clear up in July, 1949, and by the end of August, the patient had 20/30 vision. The eyeground was visible but there were still numerous vitreous opacities. By the end of September, 1949, the eyeground was well visualized without dilation and the visual acuity of the left eye was 20/20 with a $-0.5D.$ sph. $\ominus 0.5D.$ cyl. ax. 90° . The visual field with a 10-mm. white object showed normal limits.

On October 25th, the patient was again seen under homatropine dilatation. At this time, the third branch of the lower temporal vein displayed marked sheathing and a wide spot partially covered the vein about two disc

diameters from the border of the disc. There was a similar smaller spot farther down.

An area that exactly duplicated the apparent disinsertion seen first in 1948, with a slightly darker mottled appearance was separated from the rest of the retina by a definite though faint border line. The diseased vein was lying in this area. At the periphery in the upper quarter, there was an area of choroidal and retinal atrophy, evidently the result of the sclerectomy (fig. 2).

The pupil reacted well to light before dilatation was commenced. A fundus photograph was made in the New York Eye and Ear Infirmary on this day.

The following morning the patient awakened with his vision very blurred. When I saw him on October 28th at his home, he said that he had danced at some gathering on October 25th. Examination on October 28th showed that the pupil was moderately narrowed and reacted poorly to light. The fundus was faintly visible and a mass of vitreous hemorrhage could be seen in the lower part of the vitreous covering the lower half of the retina. Vision was finger counting at six feet.

The patient was admitted to Polyclinic Hospital on November 1st. Laboratory examinations, chest roentgenograms, and Mantoux test were negative. He was given atropine (one percent, three times daily), hot compresses, and eight subconjunctival saline injections between November 2nd and December 6th, on which date he was discharged from the hospital. His vision at that time was 20/100.

By March 20, 1950, his vision improved to 20/40, the fundus was somewhat hazy, and vitreous opacities could still be seen. On April 21, 1950, the vision was 20/30—, without correction; with correction, it was 20/20—. The fundus was visualized well, vitreous opacities were ill defined and few. The stippled area had disappeared, and the fundus was uniform in appearance except for two

small hemorrhages in the upper temporal quadrant.

DISCUSSION

I felt that this case should be presented and discussed because of several interesting aspects:

1. What caused the complete reattachment? It seems very unlikely that shortening the eyeball to the extent that can be achieved by sclerectomy would be sufficient in itself. The whole difference between the capacity of the eyeball before and after the operation is only two percent.

Although the mechanical explanation of retinal separation is quite simple and plausible, it leaves unexplained those many instances in which defects of the retina are outstanding, yet no separation occurs.

Why is this dreaded complication absent in, perhaps, 95 percent of the cases of senile hole-formation of the macula? Why does it not occur in about 80 to 85 percent of the cases of traumatic hole-formation? Why does it not take place in, perhaps, 85 to 90 percent of senile cystic degenerations of the periphery, where holes are definitely present?

It is generally accepted that degeneration and "detachment" of the vitreous is the first step in retinal separation. Whether this degeneration is "primary" or secondary to some known pathologic condition is not a matter of importance. In the case herein presented the vitreous was not in a normal condition, although no detachment could be ascertained. At the operation no attempt was made to seal the very large area of disinsertion. Yet, the reattachment was complete and seemingly permanent.

One wonders whether it is the sealing of the retinal tears or inflammation secondary to the trauma of operation that results in cure in the more fortunate cases. In retinal separations in which no holes were found, more or less extensive electrocoagulation of the scleral surface has resulted in permanent reattachment in many cases.

It is difficult to assess the relative merits of electrocoagulation and sclerectomy. In the case herein presented, I chose the latter procedure because the degree of separation would have required too extensive electrocoagulation, especially if the disinsertion had also been sealed. Sealing only the disinsertion did not seem at all promising when the almost complete, funnel-like detachment was considered.

Proper drainage of subretinal fluid at operation is emphasized by all authors. It seems only logical to bring the intraocular pressure back to normal or above, after drainage, by injection of normal saline into the vitreous cavity, otherwise the apposition of the retinal layers might not (or could not) be permanent.

The choice of operation in different types of retinal detachments requires extensive work and study. This case is reported with the hope that it may be a minute contribution to existing knowledge.

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GENERALIZED GIANT FOLLICULAR LYMPHOMA INVOLVING THE EYE

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A review of the literature shows giant follicular lymphoma involving the eye to be rare. Recently Chambers¹ reported a patient treated with nitrogen mustard which caused the lesion to disappear up to the time the report was written (four months later).

In his paper, Chambers¹ reviewed the subject and quoted Baehr, Rosenthal, and Klemper as saying that this type of tumor is characterized by hyperplasia of lymph follicles and spleen, absence of cytologic changes in the blood, occasional development of pleural and peritoneal effusions, absence of involvement of tonsils and lymph-

oid tissue of the gastro-intestinal tract, and occasional unilateral exophthalmos resulting from lymphatic infiltration of the lacrimal gland.

The disease has a multicentric origin in lymph follicles throughout the body; the nodes show large lymph follicles with germinal centers. Progressing slowly, the disease may remain unchanged for years and eventually terminate in Hodgkin's disease, lymphosarcoma, or leukemia.

Although the older literature included a number of cases of lymphomas involving the eye, only one report was found which mentioned lymph follicles. This was a case reported by Coats² in 1915. In this paper, he mentions two previously published cases. In none of Coats's cases, however, were enlarged regional nodes or nodes in other parts of the body mentioned.

McGavic³ reviewed 21 cases of lymphomatous diseases of the eye in the literature and found three which he called "giant follicular lymphosarcoma." All three involved the lacrimal glands; only one had other lesions—the blood picture of leukemia.

In this one generalized case—that of a woman, aged 52 years—biopsies from various sites in the body showed "giant follicular lymphosarcoma." The first biopsy was taken five years after the onset of symptoms; a year later the lacrimal gland became involved. Biopsy showed a diffused infiltration with lymphocytic cells but no follicles.

One of the cases reviewed by McGavic had been reported by Perera,⁴ who describes a lesion localized to the lacrimal gland with no enlarged nodes and showing no residuals or metastases four and one-half years following removal of the tumor and external radiation.

It may be that giant follicular lymphoma occurs more frequently than these meager reports in the literature would seem to indicate but that cases are infrequently referred to the ophthalmologist. It would seem,

therefore, of value to report the following case.

REPORT OF A CASE

History. A. B., a man, aged 69 years, came in on August 4, 1950, complaining of blurred vision in his right eye for "the past few days."

Vision was: R.E., 20/40, without correction; L.E., 20/25, without correction. He had been wearing a +1.0D. sph., O.U. He appeared to have a ptosis of the right upper lid. Closer examination showed the right upper lid to bulge forward under the supra-orbital ridge. On everting the lid, a white, slightly translucent granular mass bulged into the outer half of the right upper fornix.

Refraction showed: O.D., +0.5D. sph. \ominus +4.75D. cyl. ax. $10^\circ = 20/20$; O.S., +0.25D. sph. \ominus +0.5D. cyl. ax. $180^\circ = 20/20$.

The high astigmatism of the right eye was due to the pressure of the mass from above across the cornea; the tilt of the axis off horizontal was due to the mass pressing from the outer portion rather than straight across the eye.

The rest of the examination showed the eye to be essentially normal. It was felt that the mass had probably originated from the lacrimal gland although it might have come from the conjunctiva.

On further investigation it was found that this patient had come to Dr. R. J. Neufeld on May 4, 1950, with a complaint of "pain in the stomach." He gave a history of having had pneumonia two years previously and since then had never felt well. He appeared anemic and showed multiple enlarged

lymph nodes and was extremely tender in the area of the stomach.

Hemoglobin was 66 percent (10.30); the red blood count, 3,540,000; white blood count, 11,400 with eight percent lymphocytes, 84 percent polymorphonuclears, three percent mononuclears, and four percent eosinophils.

A biopsy of an inguinal node was done by Dr. Neufeld on May 4, 1950. The pathology report by Dr. W. S. Pheteplice showed a markedly enlarged, lobulated lymph node, measuring 4.5 by 3.0 by 2.0 cm. Section revealed homogenous gray margins of the cut surface. The center part was hemorrhagic. There was no gross evidence of necrosis.

Microscopic examination showed a lymph node with excessively large follicles at the margin and, in some places, the central areas. These follicles compressed adjacent lymphoid tissue and markedly compressed the sinusoidal tissue. The impression was of "giant follicular lymphoma."

Although it was thought advisable to take a biopsy from the mass above the right eye and then, if indicated, to treat this patient with nitrogen mustard, as had been done in Chambers¹ case, neither the patient nor his family could be convinced of the importance of these procedures. The patient died six months later. Autopsy was refused.

SUMMARY

A case of giant follicular lymphoma involving the eye, masquerading as a high astigmatism, is reported. The infrequent reports of this disease are discussed.

1820 West Third Street.

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PAPILLITIS DEVELOPING DURING CORTISONE THERAPY*

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The preliminary reports by Olson and others¹ and Gordon and McLean² in 1950 on the promising usefulness of ACTH in inflammatory diseases of the eye was followed by a widespread use of this and other steroids by ophthalmologists. As experience with these drugs widens a fuller understanding of their effectiveness for certain conditions will evolve. Likewise, their ineffectiveness for other conditions will become established through clinical trial.

Listed among the ocular diseases for which one of these steroids, cortone, is suggested by a Merck and Company brochure, is optic neuritis including retrobulbar neuritis. The purpose of this brief report is to bring attention to the fact that optic neuritis can occur during cortisone therapy for another condition. This fact may throw some doubt on the usefulness of cortisone in treating papillitis.

REPORT OF A CASE

A 70-year-old spinster had always enjoyed good health until she returned from a European trip a year ago when she developed rheumatoid arthritis. She was hospitalized and showed a gratifying response to cortisone with remission of her signs and symptoms.

Two months later there was a relapse and she was again hospitalized and treated with cortisone. This time the remission of her symptoms took longer but eventually the clinical signs subsided. The drug being scarce, it was not possible to place her on a maintenance dose.

A second relapse followed a month later and once again she was treated with oral and parenteral cortisone. It was during this relapse that her ocular condition developed.

Past ocular history revealed no previous disease. Except for presbyopia, she had no visual difficulties.

The present ocular symptoms developed during the fourth week of the second relapse already referred to, and while she was receiving 100 mg. of cortisone daily by mouth. Her first complaint was pain in the left supraorbital area accompanied by blurring of vision in the left eye. The blurring progressed very rapidly to total blindness within 48 hours. She was seen at this time.

Examination of the left eye revealed a pupil in mid-dilation with no response to direct light or consensually. Excursions of the eye caused retrobulbar pain in the left eye. There was doubtful light perception. The fundus revealed a papilledema of not more than one diopter with disc margins completely obliterated.

The disc had a watery opaque appearance indicating a considerable serous exudation into the nervehead. There were no hemorrhages. The veins were overfilled. Since the surrounding retina also showed a considerable edema, the term neuroretinitis could be applied here.

Salicylates, local heat, and atropine were ordered. Foreign-protein was withheld because the patient was already taking cortisone which was thought to provoke a similar kind of defense reaction. The right eye on the first visit was normal in all respects and an uncorrected vision of 20/30 was recorded for it.

Four days later the patient reported marked blurring in the other or right eye without associated supraorbital pain. Examination revealed the pupil in mid-dilation with very sluggish response to direct light. She stated that when looking at a person she could not see the upper half of the body. Confrontation test showed the entire upper field gone.

The fundus of the right eye revealed the upper half of the disc to be hyperemic with mild blurring of the disc margin; whereas, the lower half of the disc showed the same

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kind of watery opaque edema with completely obliterated disc margins and an extension of the edema to the adjacent retina. The veins were overfilled. There were no hemorrhages.

The left eye was unchanged from its appearance on the first visit. A diagnosis of bilateral papillitis was made, cortisone was stopped, and the patient admitted to the hospital.

The patient was hospitalized for 10 days. A complete medical survey was done which included dental, skull, and chest X-ray studies, blood chemistry, brucellosis, Mantoux, spinal fluid, and blood smears. None of these yielded any positive information. The sedimentation rate was high.

She received typhoid-H antigen intravenously, vitamin-B parenterally, nicotinic acid, and aureomycin. In spite of every effort the optic discs gradually developed a yellowish pallor and bilateral optic atrophy became established with resulting total blindness. The arthritis continued in a chronic mild form.

SUMMARY AND COMMENT

Experience with this case appears to

throw some doubt on the value of cortisone in the treatment of inflammatory conditions of the optic nerves. The patient was receiving the recommended dosage of cortisone for her arthritis, nevertheless a severe bilateral neuroretinitis developed.

If the drug has any prophylactic merit, the papillitis should not have occurred. If it has curative value one would have expected some recovery of vision.

Definite conclusions cannot be drawn from experience with one case; however, since we are confronted with a new therapeutic agent, useful information concerning it can only be accumulated through reporting isolated cases such as this.

CONCLUSIONS

1. Bilateral papillitis occurring during cortisone therapy for rheumatoid arthritis is reported.

2. The etiology of the papillitis was not established.

3. Doubt is expressed as to the value of cortisone in the treatment of inflammatory conditions of the optic nerves.

365 State Street.

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OPHTHALMIC MINIATURE

M. Cavallo records a case of a very obstinate ophthalmia cured by electrization. Many instances have occurred in my own practice, some of which appeared to proceed from a gouty disposition, in which the proper application of Electricity has operated a complete cure.

Francis Loundes, Medical Electrician,
Observations on Medical Electricity,
Printed by S. Stuart, London, 1787.

SOCIETY PROCEEDINGS

Edited by DONALD J. LYLE, M.D.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

April 2, 1951

DR. SAMUEL GARTNER, *president*

ROUND-TABLE CONFERENCE

The Treatment of Complications of Ocular Surgery

DISCUSSERS: Dr. W. Guernsey Frey, Dr. Wendell L. Hughes, Dr. Algernon B. Reese, Dr. Harvey E. Thorpe.

MODERATOR: Dr. Samuel Gartner.

Given a completely white and quiet glaucomatous eye, with an adequate filtering bleb, which has developed hypotony after iridencleisis, would you consider methods of increasing intraocular pressure?

DR. FREY replied that, if he is required to answer yes or no to this question, he would answer no. After 28 years of hospital and private practice, he has never yet seen a case, after a filtering operation for glaucoma, in which subnormal tension was a problem. Instillation of atropine may give rise to temporary increase in tension in such a case, but he would be inclined to look for a fistula. If it can be demonstrated that the aqueous is constantly leaking, it is sometimes possible to close the hole by the application of silver nitrate, other caustics, or the various electrical modalities. A conjunctival flap is rarely required.

Discussion. Both Dr. Thorpe and Dr. Hughes agreed with Dr. Frey that no treatment should be undertaken unless there is a fistula.

Dr. Reese said that he felt that hypotony was not dangerous, and that he had never seen it as the result of an iridencleisis; a trephination was more apt to cause it.

During an attempted intracapsular cataract extraction, the capsule of the lens ruptures. How would you then proceed?

DR. HUGHES answered that a capsule forceps causes a rupture more easily than an erisophake. In case of rupture, express the nucleus and wash out the remains of the mature lens. If the lens is immature, pick out the edge of the torn capsule and extract the lens. If the lens is ruptured, continue the operation as an extracapsular extraction. After the zonular ligament is ruptured, it is difficult to express the lens because of the vitreous prolapse. If there is a frank vitreous loss, do the operation as a loop extraction. If the capsule ruptures at the last moment of extraction, continue the extraction.

Discussion. Dr. Gartner asked: If one starts with a round pupil extraction and the capsule of the lens ruptures, what should one do then?

Dr. Hughes replied that the answer would depend on the maturity of the lens. If the lens is mature, an iridectomy is not necessary. In the case of a soft lens, Dr. Hughes suggested doing an iridectomy.

Dr. Frey asked whether Dr. Hughes used a fluorescent lamp to identify the lens matter. Dr. Hughes answered that the fluorescent lamp would identify soft lens matter; the capsule is only slightly fluorescent.

Dr. Thorpe said that it is important that your instruments have no burrs, and that their edges meet exactly. He suggested the use of emery paper to refinish the capsule forceps.

Dr. Reese emphasized the importance of analyzing why the capsule breaks, so that it can be prevented the next time.

Dr. Hughes said that, if the capsule breaks at the last moment, it is good to grasp it at the equator and wheel it out, so that the operation ends as an intracapsular operation.

How do you treat herniation of the hyaloid membrane into the anterior chamber following uncomplicated intracapsular cataract extraction?

DR. REESE said that we must recognize that the hyaloid is against the posterior surface of the cornea. Herniation occurs in uncomplicated cases too. There is wrinkling of Descemet's membrane and cloudiness of the cornea; the eye remains red. It is usually in the center of the coloboma. Many cases show spontaneous regression with no therapy. If a round pupil is present, Dr. Reese suggested the use of miotics and bedrest. If there is coloboma, no miotics should be used. Prolapse of the iris can result from herniation. The only way to treat a herniation of the hyaloid, which occurs 12 or more days post-operatively, is to do a posterior sclerectomy six mm. from the limbus, and then inject air into the anterior chamber.

Dr. Reese stressed that, in handling complications, it is important to meet the emergency without hesitation or temporizing. He mentioned two related conditions: (1) Hyaloid which touches the cornea and then recedes; (2) spontaneous rupture of the hyaloid, which may occur later after the operation and may lead to temporary reduction in vision and redness of the eye.

Discussion. Dr. Hughes suggested sweeping across the anterior chamber with a long curved iris spatula, then injecting air. This is done to separate the vitreous from the cornea.

Dr. Gartner asked Dr. Reese whether he had any concern of detaching the retina when doing a posterior sclerectomy. Dr. Reese replied that one should enter anterior to the ora serrata. Then to Dr. Gartner's question if herniation can cause retinal detachment, Dr. Reese replied that it cannot.

What is your procedure in the case of a highly myopic patient who has had a cataract extraction and later develops a detachment of the retina?

DR. THORPE said that he plots all the pos-

sible tears. He examines the periphery by indirect ophthalmoscopy and determines the state of the vitreous. He determines if the vitreous drags on the retina, places the patient in bed, and waits to see if the retina reattaches. If it does not, he said he does a sclerectomy, two to four mm. in width, 180 degrees or complete. The sclerectomy is combined with a diathermy barrage, using micro-pins. Dr. Thorpe said that he does not use the LaCarrera technique because it makes holes. Otherwise, the treatment is the same. In the myope the retina is usually too short for the globe.

How would you manage vitreous loss at a cataract extraction occurring: (1) Before extraction of the lens; (2) during extraction of the lens; (3) after extraction of the lens?

DR. FREY said that, in every case of cataract extraction, vitreous loss must be anticipated, and it is to minimize this danger that we employ preoperative sedation and the various methods of local anesthesia, including retrobulbar injection, and preplaced sutures. These things are routine. But in those cases in which vitreous loss is especially to be apprehended—dislocated lenses, fluid vitreous, high myopia, unruly patients—we may take special precautions.

Foremost among these precautions are general anesthesia, external canthotomy, and lid retraction by traction rather than with the speculum. Dr. Frey said that he had not personally used curare, but he thought it might be useful in such cases. The addition of hyaluronidase, 25 units, to the retrobulbar injection five minutes before making the section induces hypotony and minimizes vitreous loss.

The operation itself should be completed as speedily as possible, employing a loop, if necessary, and avoiding undue pressure either on the lens or on the globe in the course of the manipulation. After delivery of the lens, the preplaced sutures should be tied speedily and it may be advantageous to

introduce an air bubble into the anterior chamber. Dr. Frey said that he frequently sutures the lids.

Dr. Frey said that it had never been his experience that these cases require excision of prolapsed vitreous with scissors, nor had he found it necessary to employ any post-operative precautions other than those in a usual case. On the other hand, he does not allow even his best patients to walk back from the operating room nor does he operate on them in the office.

How would you treat failure of the anterior chamber to reform after: (1) Cataract extraction; (2) a filtering operation for glaucoma?

DR. HUGHES answered:

1. If, at the end of one week, the anterior chamber did not reform, he would dilate the pupil maximally with atropine, cocaine, and neosynephrine, three drops of each daily for three to four days. Frequently the anterior chamber reforms at the end of the first day of this treatment. He suggested that one should check for leakage. Dr. Hughes also suggested the application of silver nitrate (10 percent) to the wound, lightly applied for 20 to 30 seconds. At the end of two weeks, if the anterior chamber is not reformed, he suggested injecting air into the anterior chamber.

2. Dr. Hughes said that much the same treatment is used when necessary after a glaucoma operation, except the air is injected at the end of 12 to 14 days, if the anterior chamber does not reform.

Discussion. Dr. Gartner asked about the fluorescein test for gaping wounds. Dr. Hughes answered that fluorescein was very useful when put on a wound to detect leakage.

Dr. Thorpe said that formation of posterior synechias will sometimes prevent the anterior chamber from reforming. In such cases it may be necessary to do an iridectomy.

Dr. Reese said that Dr. Dunnington em-

phasized leakage and adequate suturing. He also said that he would not wait for two weeks for the anterior chamber to reform.

What is the treatment for hemorrhage in the anterior chamber after iridencleisis occurring: (1) Immediately after operation; (2) three days or more after operation?

DR. REESE said that hemorrhage in the anterior chamber absorbs very slowly, even if the tension is normal; however, if the tension is elevated, the absorption is still slower.

1. Hemorrhage immediately after operation, if small, has no significance. If there is a large amount of hemorrhage, it may be due to the fact that the major arterial circle is in the periphery of the iris instead of the ciliary body. Attempts to remove the blood at the time of the operation are usually unsuccessful. Too rapid decompression of the eye causes hemorrhage, plus sclerosis of the vessels; whereas, slow decompression of the eye will tend to prevent hemorrhage.

2. Hemorrhage three or more days after iridencleisis can be spontaneous, traumatic, or the result of massage. Hemorrhage increases the pressure and causes blood staining of the cornea. It clears in the periphery, but not in the center. Dr. Reese said that if hemorrhage is present for one to two weeks and if the tension is up, one should make a section and irrigate out the blood.

Discussion. Dr. Thorpe said that hemorrhage results from an atrophic glaucomatous iris. He said that, during the operation, he instills thrombin and adrenalin (one percent) into the anterior chamber, this reduces the amount of the hemorrhage on the operating table. In hemorrhage after the operation, he said he uses autohemotherapy (5.0 to 10 cc.) or, if hemorrhage persists or recurs, he may even give a blood transfusion.

Dr. Hughes agreed that thrombin is very helpful and said that the use of adrenalin in the anterior chamber was very good.

Dr. Gartner asked how Dr. Reese used the thrombin. Dr. Reese replied that he diluted

the thrombin (500-unit ampule) with 20 cc. saline and instilled it with the anterior-chamber irrigator.

What is the management of postoperative iris prolapse: (1) Which occurs in the first few days after operation; (2) which occurs several weeks after operation?

DR. THORPE said that if the prolapse is not covered with a conjunctival flap, he would suggest an early excision of the prolapse. If the prolapse is covered with conjunctiva, Dr. Thorpe said he would suggest the use of pilocarpine and eserine for 48 hours. If the iris is pulled back, Dr. Thorpe suggested suturing of the wound; if the iris is not pulled back, he suggested that the conjunctival puncture be dissected at the root. Dr. Thorpe reported poor results with trichloroacetic acid and he has, therefore, been using diathermy. In cases of late iris prolapse, Dr. Thorpe said that he dissects the conjunctival flap and frees the iris from the bed.

Discussion. Dr. Frey said that in dissecting the conjunctiva down, it is difficult but important to free the iris. He asked Dr. Thorpe whether he used nonpenetrating cautery. Dr. Thorpe replied that he used actual cautery and usually got a red eye.

Dr. Gartner asked if there was any danger in leaving a small prolapse alone. Dr. Thorpe replied that there was no danger so long as the prolapse was not of the balloon type.

Dr. Gartner then asked why a prolapse is considered so bad when it follows a cataract operation, but not after an iridencleisis. Dr. Thorpe replied that a prolapse after a cataract extraction is considered serious because of the danger of glaucoma. Secondly, it is dangerous because leaving the iris in the wound may cause sympathetic ophthalmia, and, thirdly, a prolapse after a cataract operation produces astigmatism.

Dr. Reese said that it is not the fact that the iris is in the wound that is so dangerous, but how it is in the wound. After a cataract operation it is knuckled, but after

an iridencleisis it acts as a wick.

If a patient on the operating table becomes unruly and difficult to manage just before the operation, how would you proceed?

DR. FREY said that, if the operation is an elective one, it should be deferred. Investigation may reveal that the preoperative medication has had a stimulating effect rather than a sedative effect. At the next attempt, another medication can be used. Possibly more to the point would be to consider general anesthesia in such a case.

If the surgery is necessary (acute glaucoma), it may be advisable to use intravenous general anesthesia then and there. In certain cases when the surgeon is convinced that the lack of self-control on the part of the patient is truly an unnecessary display, and the surgery is such that this restlessness will not interfere with the end result (muscle operation, cyclodiathermy (and so forth) it may be permissible to employ "vocal anesthesia." As practiced in Vienna, it may consist of a clip on the ear and a "Halt's maul." Or the surgeon may proceed quite regardless of the demonstration if he is convinced that the anesthesia is adequate.

What is the treatment of postoperative intraocular infection, for example, in iridocyclitis, endophthalmitis, corneal abscess?

DR. HUGHES replied that he uses 50,000 units of penicillin subconjunctivally in all intraocular operations. He maintained that an intramuscular injection of penicillin is of no value.

In iridocyclitis due to too much atropine, he suggested a change to hyoscine. He also suggested use of foreign protein and cortisone drops.

In endophthalmitis, Dr. Hughes advised use of subconjunctival injections of penicillin daily, or intravitreal injections of penicillin, or penicillin by iontophoresis.

For abscess of the cornea, Dr. Hughes suggested the same treatment as for endophthalmitis.

Discussion. Dr. Thorpe said that in en-

dophthalmitis he uses intramuscular injections of ACTH. Prior to this, however, he does a Thorn test to determine if the patient reacts to ACTH. In traumatic cases with infection, he said that he uses ACTH in addition to antibiotics.

Dr. Frey discussed the use of the thermophore in corneal abscesses.

What is the management of an eye with epithelial downgrowth into the anterior chamber after cataract extraction?

DR. REESE replied that there are two ways that epithelial downgrowth may occur:

1. As a localized cyst caused by implantation of epithelium at the operation. These cysts are treated by local excision, by injection of a little diluted iodine into the cyst, or by X-ray therapy.

2. As downgrowth, which may be prevented by adequate toilet of the wound and eversion of the conjunctival edges. Diagnosis of this condition is difficult since many other conditions simulate it. Vascularization of the cornea is a feature of this condition. Therapy is usually X-ray irradiation, and Dr. Reese reported that out of 24 cases he had seen, about 50 percent were treated successfully with X rays.

Discussion. Dr. Hughes said that the type of suture which pulls on the conjunctiva will cause epithelial cysts. The type of suture which pulls on the edges of the wound tends to fold in epithelium and may produce cysts or epithelialization of the anterior chamber.

Dr. Frey asked Dr. Reese why the X-ray irradiation which destroys the downgrowth does not destroy the surface epithelium. Dr. Reese replied that the young epithelium is more sensitive to the X rays.

How do you manage a case of detachment of the retina when, after operation for any reason, as psychosis, cardiac decompensation or asthmatic attack, it becomes necessary for the patient to sit up? Does this necessarily seriously endanger the success of the operation?

DR. THORPE replied that he permits his patients to sit up in cases of cardiac decompensation. In psychosis, he said, the eyes will continue, after closure of both eyes, to roll, and he therefore suggested the use of pinhole glasses in such a case. He said that he had had no experience with asthmatics in this situation.

Discussion. Dr. Reese said that, in time, we will allow all cases of detachment up earlier, perhaps four to five days postoperatively. Dr. Frey suggested 24 hours as a likely period. Dr. Thorpe said that an ideal patient should be allowed up in two weeks. Dr. Reese said that he considers 10 days to be sufficient.

After cataract extraction, the iris is drawn up into the wound and the pupil gradually becomes smaller and smaller, due either to iritis or prolapse: How would you go about enlarging the pupil?

DR. FREY said that this is a case, above all others, for the employment of the Wheeler knife with discission entirely through the iris. Usually the area at the limbus above, where the knife is introduced, is already gray from the previous surgery, and the opening in the iris and in the pupillary membrane is behind clear cornea. Vitreous generally prolapses into the anterior chamber and keeps the iris wound open. If a fine secondary membrane forms in the opening, it can be dealt with later with a Ziegler discission.

Other methods of procedure are keratome incision and the use of the De Wecker scissors, or a punch. If a punch is used, the surgeon must be sure that the piece of the membrane has been completely excised; if the instrument is not very sharp, a few uncut fibers may result in avulsion of the iris upon withdrawal of the punch.

For any of these procedures it is wise to have the eye previously ischemic through the instillation of strong neosynephrine to prevent bleeding and clot organization in the pupillary opening.

How would you manage the following

complications of corneal transplant operations: (1) Swelling and expulsion of the corneal graft; (2) Tilting of the corneal graft?

DR. HUGHES replied that swelling of the corneal graft is not uncommon. He suggested in most cases leaving the eye alone and, if the swelling is marked, he mentioned the use of cortisone drops after five to six days.

As regards expulsion of the graft, Dr. Hughes said that about 10 days postoperatively, providing there is no infection, he usually performs a regrant and makes a conjunctival flap over the cornea. If iris is present, he excises it.

In cases of tilting of the corneal graft, Dr. Hughes said that it should be left alone, and it will usually flatten out itself. He also suggested the use of cortisone drops for 10 to 12 days postoperatively.

Discussion. Dr. Gartner asked about the frequency of corneal transplant operations to which Dr. Hughes replied that at the New York Eye and Ear Infirmary about 25 to 30 cases are done each year.

How would you proceed with a glaucoma operation if the lens capsule is accidentally perforated during the course of the surgery?

DR. REESE replied that, if the perforation is appreciated at the time it occurs during the course of the operation, he would proceed immediately with the extraction of the lens. He said he would enlarge the incision with scissors, perform an iridectomy, and extract the lens.

Sutures should be applied at each edge of the original glaucoma incision according to the method described by Perera. At the completion of the operation try to leave a pillar of the iris in the wound on one side or both sides thus producing an iridencleisis.

If the perforation of the lens capsule is recognized later during the postoperative convalescence, Dr. Reese said he would proceed immediately with the extraction.

How soon is reoperation indicated, and what type of procedure offers the best prognosis when there is a rise in ocular tension

after iridencleisis occurring: (1) Soon after the original operation; (2) several weeks after the original operation?

DR. THORPE said that in narrow-angle glaucoma, the rise in tension is sometimes the result of an intumescent lens and sometimes is caused by edema of the vitreous. He suggested the use of ACTH intramuscularly. However, in cases of frank glaucoma, he suggested doing a peripheral iridectomy to one side of the iridencleisis. He said he would reopen the wound, enlarge it, and do a sclerectomy. In the wide-angle type, Dr. Thorpe said he usually does a trephination.

In cases in which the rise in tension occurs several weeks postoperatively, Dr. Thorpe suggested similar measures to those mentioned for narrow-angle glaucoma—peripheral iridectomy and iridencleisis with sclerectomy. In wide-angle glaucoma, he suggested a cyclodiathermy or electrolysis.

What is the method of choice for removal of a mature cataract which has developed after a filtering operation for glaucoma?

DR. FREY said that, although most surgeons are very apprehensive about these cases, they are really quite easy to deal with. A small corneal section should be made in front of the filtering bleb, with either a pre-placed corneal suture or with immediately placed edge-to-edge appositional sutures, and the small incision is then enlarged with scissors.

It is imperative that the lens be removed within the capsule. Loss of a small amount of vitreous is of little consequence compared with the dangers of retaining any cortical matter. Fortunately, these lenses are easily removed in the capsule, even when there are adhesions of the iris to the anterior lens capsule. Such adhesions should be separated with a spatula and the lens should then be removed with pressure and traction, or even with the loop.

Many of these lenses are slightly subluxated, perhaps because of the previous glaucoma surgery, and this may be one of the reasons why the cataract developed so

rapidly. Dr. Frey said it has been his experience that the tension remains down in these cases after extraction of the cataract without use of miotics, where previously miotics may have been required.

What is the treatment for a socket from which an orbital implant has been extruded or from which it has become necessary to remove an orbital implant?

DR. HUGHES said that in such cases one should then use a buried implant, since the integrated implant has already given trouble. He also stated that he no longer uses a vitallium implant; he now prefers the plastic implants.

In a diabetic is the complication of hyphema and vitreous hemorrhage after a filtering operation preventable? If not, how would one treat it?

DR. REESE replied that, at the time of operation, he would inject a large amount of novocaine retrobulbarly with the idea of re-

ducing the intraocular pressure as much as possible. At the time of the operation, he would try to decompress the anterior chamber slowly. If hemorrhage occurred, it should be treated the same way as any postoperative hemorrhage.

Discuss the management of glaucoma after a cataract extraction.

DR. THORPE said that he used a cyclodialysis operation for glaucoma following a cataract extraction. He also uses cortone drops locally. If the increase in tension is due to a round pupil, he suggested the use of neosynephrine and homatropine. In some cases, he said, he transfixes the iris and performs a partial or complete iridectomy. In such cases it is important to look for intraocular tumors.

Discussion. Dr. Hughes said that cyclo-electrolysis is valuable in such cases.

Bernard Kronenberg,
Recording Secretary.

OPHTHALMIC MINIATURE

Medicinal Powders made from Precious Stones

In the name of Christ take some pearls and reduce them to fine powder in a brass mortar. This preparation is valuable in faint nebulae in front of the pupil that appear like a translucent cloud in a clear sky. The following remedy is also useful for the same trouble: Take some rock crystal and reduce it to powder, as just described. Another: Take the stone called jasper and reduce it to a fine powder. It is efficacious if the eye becomes red and engorged with blood, since it relieves it and any other form of blood-red pannus. Another remedy for the same ailment is red coral reduced to a very fine powder. It will expel the excessive blood and clarify the vision. Another prescription: Reduce sapphire to a fine powder. In this condition it is of great value in nebulae, because it not only removes the cloudy deposit but also opens the vitreous, contracts the pupil, and clarifies the whole eye. You will find the result very satisfactory. Again, take some of the stone called amadine, powder it, and apply it to the eye for nebulae. Take jacinth, jasper, and talc; powder and mix them thoroughly. Dusted into the eye, they will corrode pannus, clarify the eye, and refresh the visual spirit. In the same way, prepare betellus, to be used in precisely the same manner as the previous preparations. It will be found to act like them.

Benevenutus Grassus of Jerusalem,
De Oculis Eorumque Egritudinibus et Curis,
Translated by Casey A. Wood, 1929.

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THE RESIDENCY TRAINING SYSTEM AND MEDICAL INSURANCE PROGRAMS

The residency system in the teaching and special hospitals is the core and backbone of graduate medical training. Graduate medical training must be sharply differentiated from postgraduate training. Graduate training is the instruction and training given the young physician immediately after graduation when he serves as a resident member of a hospital staff—as intern, assistant resident, resident, or as an extern or fellow. Postgraduate education may be defined as the instruction given

practicing physicians and is provided by special or refresher courses, medical society meetings, and the like.

In the modern residency system the new graduate in medicine begins his service as intern or house-officer and under the guidance of his chief-of-service and seniors gradually learns the applied technique of his chosen specialty. Didactic instruction in the so-called basic sciences is only a supplement to the all-important clinical training. As he

becomes proficient in his clinical specialty, he passes through the various grades of assistant resident and finally reaches the grade of resident, where under his chief and seniors he has direct responsibility for the care of patients. In surgery and the surgical specialties he obtains his surgical training first by assisting in operations, and later as he becomes proficient, himself operating on patients. While he may act as assistant to the visiting staff on their private and semiprivate patients, his own operative training is derived usually from patients in the public-ward service of the hospital.

The residency system in surgery was introduced in America by the late William Stewart Halsted and gradually supplanted the old apprentice or preceptorship method of graduate training. In 1901, the residency service in The Johns Hopkins Hospital was the only fully developed such service in surgery. In 1941, there were 30 residencies patterned after it. In 1951, there were 130 such services in surgery in the (civilian) hospitals of the United States. The same trend toward the residency system has taken place in the special ophthalmic hospitals and in the departments of ophthalmology in the university teaching hospitals. The old preceptorship system has gradually disappeared until now only vestiges of it remain. The residency system has been extended until it now generally covers a minimum period of three to five years.

In order for any residency system to function properly there must be a steady flow of public ward patients to provide the material for training. The ward population in the present American teaching or special hospital stems from three main sources: (a) From indigent patients who come of their own volition to the out-patient department to seek medical aid. This is the chief source of supply. (b) From patients in the lower-income brackets who are referred by their own personal physicians. (c) From patients with difficult diagnostic or therapeutic problems who come to the teaching or special hospital

because of its unusual facilities, and the superior care afforded.

It is undeniable that the average ward patient in a properly conducted teaching or special hospital, by and large, receives the best of professional care. The chief of clinic and his associates are men selected and chosen on account of their clinical ability and scientific distinction. The resident and senior assistant-residents are all men who have had several years' training with the major problems of their specialty. The resident staff has at hand the best of modern diagnostic and therapeutic equipment. Through constant practice they have become skilled technical surgeons. The resident surgeon or senior resident ophthalmologist, with his daily operative schedule, is undoubtedly at the peak of his skill as a technical surgeon, and is usually technically superior to the older, visiting surgeon who operates much less frequently. The resident staff has available unlimited consultation service. Thus, in supervision and direct care, the ward patients have every advantage and facility available to the private or semiprivate patient, regardless of what professional fee he may pay. Indeed, if the private physician or specialist does not have the privilege of admitting his patients to the teaching or special hospitals, the average ward patient in such hospitals probably receives better medical care than the private patient elsewhere. And yet the integrity of the residency system, vital for the training of the surgeon and specialist of tomorrow, and beneficial to the patient, is threatened and endangered by the social changes of today, by the changes in the pattern of medical practice, and especially by the insurance programs.

The growth of the Blue Cross and Blue Shield, the medical care of veterans and their dependents, the group medical insurance plans of large industrial corporations and unions, all the various forms of voluntary medical care insurance, and the specter of compulsory medical insurance, all carry with them a threat to the residency system.

Whether one approves or disapproves of voluntary or compulsory medical care insurance is not the question—all have the common denominator of providing a fee-for-service for the group of patients, a great number of whom were formerly ward patients and on whose care our residency system is based.

Blue Cross insurance pays to the hospital the full cost of semi-private care. A patient who heretofore had paid his way in the public ward is thus automatically relieved of all usual hospital bills and with the present high employment and high wages, he is now more than ever prepared to pay the charges of a private or personal physician. Thus he is immediately removed from the ward service. The Blue Shield and various other plans of voluntary insurance go further and pay a guaranteed fee-for-service to the private and personal physician. Thus the ward population is rapidly being reduced to those in the lowest income bracket, the unemployed, and those unable to afford the luxury of either Blue Cross or Blue Shield insurance.

The veterans hospitals, already providing medical care for a large segment of our population, still further divert patients from the public wards.

The insurance plans of large corporations and unions do likewise. Many of our ward patients of yesterday are our semiprivate patients of today. Although this movement may be, and probably is, quite commendable from the sociologic point of view, it is doubtfully beneficial to the patient, and, as the facilities for training surgeons and specialists are further curtailed, will damage the residency system graduate training, will result in poorly trained doctors graduating from the hospitals, and will ultimately militate against good medical care for the patient.

Dangerous as this shift of ward population to the semiprivate class may be to graduate education, it is not unwelcome by hospital managements. The hospitals today are sick. Confronted by the rapidly mounting cost of

medical care, by payrolls mounting each day and the scale yet lagging behind that of industry, by increased charges for everything they buy, the hospitals have steadily increased their charges to patients until they are now threatened by the law of diminishing returns. Small wonder they are happy to transfer ward beds, which even with state-aid pay only a fraction of their cost, over to the category of semiprivate beds where costs are met by some insurance plan. Their endowments have not increased. Private philanthropy is drying up under the taxation load. Deficits have reached frightening figures. It is a fight for survival. Regretful as it may be, the ward service in the teaching hospitals is being curtailed more and more.

As insurance plans grow in breadth and scope, the ward population threatens to be limited to (a) those in the lowest economic status, supported partially by state and civic aid, (b) the few patients referred by conscientious physicians who abrogate their fee-for-service that their patients may obtain better care, and (c) the very few patients who eschew a private doctor in order to avail themselves of the facilities and after-care offered by the ward service. Even an optimist can scarcely hope to keep the public wards full with the latter two classes and, with the increasing prosperity, the first class daily grows smaller.

If the present trend for the transfer of ward to semiprivate beds continues, the question of whether the present residency system can be continued must be met. It obviously cannot be continued as it is at present if the public ward services grow smaller and approach the vanishing point. Shall it be continued on a smaller scale and an increasing number of our interns and assistant residents be transferred to the semiprivate services, there to serve as assistants to the visiting physicians, to gather up such crumbs of experience and responsibility as they may be able—a return to the old preceptorial system? Such a solution would not be a universally happy one, and the educator of today can

feel but sorrow for the surgeon and specialist of tomorrow. Is there any other solution?

The importance of the problem has been widely recognized. The questions of the admission of insured patients to the public ward services and the disposition of any fee-for-service paid have been subjects of consideration by committees of special surgical societies and some state medical societies. There appears to be a unanimity of opinion that the freedom of choice of the patient to enter either the public or semiprivate ward should not be interfered with for the mere reason that he holds hospital or medical care insurance. It has been suggested by one such committee that, when patients with hospital or medical care insurance apply to a hospital for admittance, they be informed of their freedom of choice, but that those patients who previously had no private physician, or who are unlikely to be able to employ a private physician for the postoperative care after their discharge from the hospital, be advised to elect the public ward service and treatment by the resident staff.

This appears to be sound reasoning, and certainly is calculated to conserve to the practicing physician the bulk of the more affluent insurance-covered patients. It would also be quite agreeable to the hospital management, even though any fee-for-service were segregated for some special purpose not connected with the support of the hospital. Would such a scheme, however, repopulate the ward beds and insure the continuity of the present residency system? It seems quite improbable that it would. Such a system is already in practice in many teaching hospitals manned by both full-time and part-time staffs. Immediately the element of competition for the insured case complicates the picture with varying degrees of embarrassment to the residency training system. If the question is to be fully solved, a more frontal attack will probably be necessary.

The one obvious solution is for the teaching and special hospitals with well-developed and established residency systems to con-

tract with the insurance companies for the care of their clients. If the semiprivate status of the patients is to be maintained, then some public wards might be remodeled to provide more attractive facilities and the senior residents taken out of white uniforms and promoted to the rank of associates. The ward services would thus be somewhat camouflaged, but nevertheless would remain essentially the ward services they now are.

Such a straightforward acknowledgement of the situation and open-and-above-board contract would solve the problem, provided an educational campaign would make it acceptable to the insured clients of the voluntary insurance companies, to the corporations and unions with insurance plans, and to the medical profession. It would save the residency system, continue to provide the best of care for the patients, solve the financial plight of the teaching and special hospitals, and quite probably permit lower insurance premiums for the patient.

Such a program would appear to be putting these hospitals squarely in business. It would almost undoubtedly raise the cry of "unfair competition" from many practicing physicians. It would further rouse the ire of the radiologists and anesthesiologists who are already indignant at the presumption of hospitals encroaching on their fields of activity. It would appear to fly in the face of the Hess Committee report and the "Revised principles of medical ethics" of the American Medical Association. Chapter III, Article VI, Section 6 of these "Revised principles" states that "A physician should not dispose of his professional attainments or services to any hospital, lay body, organization, group, or individual, by whatever name called or however organized, under terms or conditions which permit exploitation of the services of the physician for the financial profit of the agency concerned."

If the teaching and special hospitals entered into contractual relations with insurance companies for the express purpose of salvaging their residency systems and con-

tinuing their present graduate training and programs, the cry of "unfair competition" would probably die a natural death. More serious would be the apparent conflict with the recently adopted Hess Committee report and the "Revised principles of ethics" of the A.M.A. It should, however, be noted that the pertinent clause contains the words "for the financial profit of the agency concerned."

If any fee-for-service collected by the hospitals were segregated in a special fund for medical research, or a fund for the furtherance of graduate medical training, or to provide adequate remuneration for the now underpaid resident staffs, and thus did not accumulate for the financial profit of the hospitals, such an arrangement might meet both the letter and spirit of the "Revised principles." This might well be a matter for decision by the Judicial Council of the A.M.A.

The cry against hospitals going directly into the business of the practice of medicine is after all something of a red herring. One has only to glance at the charges made against patients for the services of hospital-employed anesthesiologists and radiologists, all of which usually are collected and retained by the hospitals. One has only to realize that fees collected for professional services rendered by a university full-time staff are as a rule used for the support of the department earning such fees. To a somewhat limited extent the hospitals and many university clinical departments are already in business. The question is simply one of degree.

If this proposal should not prove feasible, then perhaps some more palatable substitute might be worked out. The essential thing is to realize that all insurance programs for medical care, be they voluntary or compulsory, together with changing economic conditions, contain a threat to the integrity of our residency training programs.

This threat is real and not fancied. In many parts of the country the attendance in the out-patient departments is on the wane. There are no longer long waiting lists for admittance to the public wards, and in many of our ophthalmic hospitals our public wards

are only partially filled. At the same time the demand for semiprivate accommodations is growing by leaps and bounds. The semiprivate beds are all filled and there is a long waiting list for admittance.

The chiefs of clinics in ophthalmology are already scouring the high-roads and the hedges, the outlying private hospitals, and city- and state-supported institutions, for operative and clinical material for the training of their resident staffs. If the present trend continues, and there is every indication that it will continue, unless some frontal and direct measures are taken, the integrity of our graduate residency training systems will be damaged and possibly destroyed.

Alan C. Woods.

WILLS EYE HOSPITAL FOURTH ANNUAL CLINICAL CONFERENCE

Approximately 350 ophthalmologists attended the fourth annual clinical conference of the staff and ex-residents held at the Wills Eye Hospital, Philadelphia, on March 21 and 22, 1952.

Dr. L. Pellman Glover presented a paper on "Pheochromocytomas: Emphasis on eye symptoms, especially in children." He described a case which was cured after removal of the tumor of the adrenal.

An improved model of his muscle tucker was presented by Dr. William J. Harrison.

Dr. Edmund B. Spaeth spoke on "The surgical aspects of defective abduction." He recommended tendon transplant in the acquired type for functional improvement of the paralyzed muscle.

Based on a survey of 150 cases, Dr. James S. Shipman, Dr. James H. Delaney, and Dr. R. H. Seely emphasized the anterior route for extraction of intraocular foreign bodies less than three mm. in size. Dr. Shipman stated that he relied more on the Sweet geometric method of localizing intraocular for-

eign bodies. The Berman locator had proved of little assistance to him.

A symposium on "Wound closure" included a review by Dr. Howard F. Hill of types of incisions and sutures in cataract surgery. Dr. Wilfred E. Fry advocated the use of "track" sutures for a more secure closure to minimize complications, preferring silk to catgut sutures. Dr. I. S. Tassman described the use of plasma, thrombin, and hyaluronic acid as added safety factors for corneal wound closure and healing. Dr. Perce De-Long presented evidence and results in microscopic sections of animal eyes, showing that fibroblastic proliferation occurs within 48 hours. He also showed that in all treated eyes there was positive evidence that healing and repair of corneal wounds was stimulated and accelerated.

Dr. Irving H. Leopold and Dr. Thomas G. Dickinson gave an interesting discussion on "Antihyaluronidase antistreptolysin titres in uveitis." A search, they feel, for the antibodies developed by the body against substances produced by the streptococcus organism may help in the diagnosis of the basic cause of uveitis.

A report of studies made with some of the newer drugs in the hospital's research laboratory by Dr. Leopold and his associates revealed:

1. Autonomic ganglion blocking agents, when administered parenterally—that is, by intramuscular or intravenous injection—will produce a lowering of intraocular pressure in normal eyes. This suggests, they feel, that these agents may be of value in the treatment of glaucoma. In their studies they have also shown that agents which are frequently used for the relief of patients with peptic ulcers may produce elevations of intraocular pressure, that is, these agents may precipitate glaucomatous attacks. It is possible they point out, by virtue of these studies, that several of these agents may be superior to ones which are presently available for refraction of the human eye.

2. Dilute di-isopropyl fluorophosphate (DFP) seems to fulfill some of the require-

ments of the ideal miotic agent in that it requires fewer instillations than the commonly employed drugs and produces less variation and less fluctuation in the daily pressure curves. They have found urecholine to be a potent miotic agent. It appears to be equally as effective in the control of mild chronic simple glaucoma as other agents available to date.

3. There was no significant difference between compound F and cortisone as an anti-inflammatory agent when tested experimentally. However, their clinical studies have shown that compound F may be more effective than cortisone in some types of ocular inflammations, particularly in severe vernal conjunctivitis, in cases of uveitis, and in other ocular inflammations such as episcleritis and phlyctenular disease.

Staff doctors who assisted in these studies were: A. H. Keeney, C. R. Mullen, B. Gettes, C. Steinmetz, A. Cleveland, F. Frisch, J. Deichler, P. R. McDonald, R. Mulberger, and A. Vogel.

Dr. Derrick Vail delivered the Arthur J. Bedell Lecture. His subject was "Zonule membrane and cataract expression." His thorough covering of the subject from the embryologic and anatomic standpoint made the practical approach to his remarks on cataract expression most interesting and enlightening.

Another important feature of the conference was the presentation of eye surgery in color television, through the courtesy of Smith, Kline, and French Laboratories. Included among the nine operations which were viewed with great interest by those in attendance was a Ridley plastic lens implant in a case of cataract extraction.

Two interesting clinical pathologic presentations were made by Dr. William H. Annesley, Jr., and Dr. James H. Parker.

The meeting was not without its social aspects. A cocktail party and informal reception for the doctors and their wives were held at the Barclay Hotel, Friday evening, followed by a delicious dinner.

Kenneth L. Roper.

CORRESPONDENCE

CILIA AND OINTMENTS IN ANTERIOR
CHAMBER

Editor,

American Journal of Ophthalmology:

Eternal vigilance is the price we must pay for freedom from ophthalmic complications. Dr. Derrick Vail has expressed opinions in his fine paper ("Lint in the anterior chamber following intraocular surgery." *Am. J. Ophth.*, 34:1533 (Nov.) 1951) that agrees with my teaching that every mistake in eye surgery is avoidable. With every change in operating-room personnel, I allot time for directions to keep dry cotton far from the instrument tray. Fortunately, surgeons who operate with magnifying loupes can detect lint and cilia often overlooked by residents and nurses.

Dr. Vail referred to the danger of cut eyelashes in the anterior chamber but could not cite an actual occurrence. I trim the upper-lid lashes with anointed scissors prior to cataract surgery. From the number of cilia I have seen severed accidentally by surgeons, who do not follow this procedure, it seems strange, no reference can be found in our literature, that any of these loose foreign bodies ever entered the anterior chamber.

Shortly after the presentation of Dr. Vail's paper, I published an article, "Cilium in the anterior chamber" (*Arch. Ophth.*, 44:424-428 (Sept.) 1950). My case, like that reported by Sitchevska and Payne, resulted from a penetrating wound. From our review of the literature, the condition appeared to be extremely rare although I was able to collect 13 additional cases from four ophthalmologists.

My main interest at the time was to ascertain if the cilia had been removed from the anterior chamber. Despite Wurdemann's clear indications for removal, 10 patients were allowed to retain the foreign bodies without subsequent irritation. One of my contributors admitted that, in two patients, cilia lodged in the anterior chamber after in-

traocular surgery. Apparently this clinical occurrence is considered unimportant or too embarrassing to report in the literature. One statement in my paper intimated that anterior-chamber foreign bodies catalogued by hospitals do not include cilia. A large eye institution informed me that not a single case of eyelashes in the anterior chamber, following surgery or penetrating wounds, could be found in records reviewed since 1928!

The impressive summary in Dr. Vail's paper is marred by a ban on ointments post-operatively. He referred to my 1948 communication regarding the management of ointment in the anterior chamber after cataract extraction. Since watertight suture closure is now universally employed by recognized eye surgeons, this complication can be discounted. I would rather risk that remote and harmless possibility than forego the use of nonallergenic antibiotic ointment. I fear infection more than ointment.

How quickly statements of authorities like Dr. Vail are accepted as gospel truths was demonstrated at the January meeting of the New York Academy of Medicine, Section on Ophthalmology, when a speaker quoted his ban on the use of ointments. The students' vision for therapy becomes blurred when their teachers disagree.

(Signed) James W. Smith,
New York, New York

BOOK REVIEWS

CLINICAL PATHOLOGY OF THE EYE. By Bernard Samuels, M.D., and Adalbert Fuchs, M.D. New York, Paul B. Hoeber, Inc., 1951. 420 pages, with 418 illustrations, 191 in full color. Price: \$20.00.

The need for a more detailed English textbook on eye pathology has been apparent for many years. The excellent early works of Parsons (1907) have not been reedited, and that of Friedenwald (1934) very rapidly passed out of print and has not been re-

issued. During subsequent years several texts were published, but most students and teachers have felt they were either too simplified and incomplete or lacked proper descriptive detail. The purpose of the present book is to bring the essential parts of the pathology of the eyeball into usable and convenient form, and it is designed for use by students and teachers and for reference by general pathologists and surgeons. It is based on the clinical and pathologic experience of the authors at the New York Eye and Ear Infirmary and at the Allgemeines Krankenhaus in Vienna.

Most of the illustrations are based on drawings of pathologic changes in the eye rather than microphotographs, and the beautiful color plates are the same as those used in Adalbert Fuchs's *Atlas of Histopathology of the Eye*.

A standard method of presentation is used, the book being divided into 14 chapters, as follows: General pathology, cornea, uvea, sclera, lens, retina, optic nerve, vitreous body, myopia, tuberculosis, syphilis, postoperative pathologic findings and their complications, injuries, and tumors. This method of presentation results in some difficulties unless the author is inclined to add separate chapters. As an example, hydrophthalmos is included in the chapter on the cornea, and the discussion on glaucoma is found in the chapter on the optic nerve. It is unfortunate that the material in this book is restricted to a discussion of the pathology of the eyeball. Pathologic changes in the lids and lacrimal apparatus, conjunctiva, and orbit are omitted.

The authors have decided to rely on a terminology which is "in line with tradition and international usage." At some points in the book this is unfortunate for other teachers and especially for students who must continue to cope with double systems of nomenclature, and it is hoped the authors will decide to alter the terminology in future editions to coincide with that in general use.

The chapter on general pathology (mostly general eye pathology) is excellent and in-

cludes a description of inflammation and its application to various diseases of the eye. Vascular diseases such as atherosclerosis, arteriolosclerosis, and phlebosclerosis are incompletely covered. A discussion of changes due to age includes a description of pingueculum and pterygium, which might better be considered under degenerations.

The sections on the cornea and uveal tract are fairly complete, and very adequate for the average ophthalmic student. The authors have reversed the usual method of teaching in their discussion of some conditions of the retina. They present the ophthalmoscopic and pathologic significance of large white areas, medium white patches, small white patches, scintillating dots, white streaks, lines and strands, yellowish patches, red spots and dots, brownish spots, black spots and dots, and gray patches.

This method of presentation of the various manifestations of individual lesions is good. It fails, however, to show in serialum, the course of the lesion and its effects upon the retina and the coincident lesions in other portions of the retina which are so important for diagnosis of many diseases. The student has a better perspective if he learns the early, moderately advanced, and advanced stages of an individual disease rather than trying to interpret the character of a particular lesion.

Some vascular and degenerative conditions of the retina are omitted or incompletely described. The discussion on optic neuritis is limited to a brief and incomplete presentation of inflammation of the disc. Methods of repair in lesions of the optic nerve are completely omitted. The authors differentiate papillitis from neuritis and papilledema, stating that the term papillitis should be reserved for indefinite cases in which a distinction cannot be made. This concept is not universally accepted either clinically or pathologically.

The chapters on postoperative pathologic findings and injuries are quite well done and sufficiently complete that the student obtains an excellent perspective of changes in the

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A standard method of presentation is used, the book being divided into 14 chapters, as follows: General pathology, cornea, uvea, sclera, lens, retina, optic nerve, vitreous body, myopia, tuberculosis, syphilis, postoperative pathologic findings and their complications, injuries, and tumors. This method of presentation results in some difficulties unless the author is inclined to add separate chapters. As an example, hydrophthalmos is included in the chapter on the cornea, and the discussion on glaucoma is found in the chapter on the optic nerve. It is unfortunate that the material in this book is restricted to a discussion of the pathology of the eyeball. Pathologic changes in the lids and lacrimal apparatus, conjunctiva, and orbit are omitted.

The authors have decided to rely on a terminology which is "in line with tradition and international usage." At some points in the book this is unfortunate for other teachers and especially for students who must continue to cope with double systems of nomenclature, and it is hoped the authors will decide to alter the terminology in future editions to coincide with that in general use.

The chapter on general pathology (mostly general eye pathology) is excellent and in-

cludes a description of inflammation and its application to various diseases of the eye. Vascular diseases such as atherosclerosis, arteriolosclerosis, and phlebosclerosis are incompletely covered. A discussion of changes due to age includes a description of pingueculum and pterygium, which might better be considered under degenerations.

The sections on the cornea and uveal tract are fairly complete, and very adequate for the average ophthalmic student. The authors have reversed the usual method of teaching in their discussion of some conditions of the retina. They present the ophthalmoscopic and pathologic significance of large white areas, medium white patches, small white patches, scintillating dots, white streaks, lines and strands, yellowish patches, red spots and dots, brownish spots, black spots and dots, and gray patches.

This method of presentation of the various manifestations of individual lesions is good. It fails, however, to show in seriatum, the course of the lesion and its effects upon the retina and the coincident lesions in other portions of the retina which are so important for diagnosis of many diseases. The student has a better perspective if he learns the early, moderately advanced, and advanced stages of an individual disease rather than trying to interpret the character of a particular lesion.

Some vascular and degenerative conditions of the retina are omitted or incompletely described. The discussion on optic neuritis is limited to a brief and incomplete presentation of inflammation of the disc. Methods of repair in lesions of the optic nerve are completely omitted. The authors differentiate papillitis from neuritis and papilledema, stating that the term papillitis should be reserved for indefinite cases in which a distinction cannot be made. This concept is not universally accepted either clinically or pathologically.

The chapters on postoperative pathologic findings and injuries are quite well done and sufficiently complete that the student obtains an excellent perspective of changes in the

eye which result from surgical and mechanical trauma.

The section on tumors includes a discussion of both benign and malignant tumors affecting various portions of the eye. In the discussion on malignant tumors of the choroid the usual pigmented tumor is called a melanosarcoma but it is believed by many observers at the present time that malignant melanoma is preferable because it does not imply an origin from a specific tissue. An attempt is not made in the discussion to grade these tumors on the basis of cytologic characteristics or reticulum content for prognostic purposes.

This book is highly recommended for use in laboratories engaged in active teaching and by individual students who wish to gain an insight into the subject of eye pathology. It is the best English text on the pathology of the eyeball which has appeared for many years.

Michael J. Hogan.

A MANUAL OF ORTHOPTICS. By Julia E. Lancaster. Springfield, Illinois, Charles C Thomas, 1951. 200 pages, Price: \$5.50.

Miss Lancaster, who has a master's degree in education, presents orthoptics as a pedagogic problem stating that the eye-training program proceeds as steps in the learning process.

The book offers a description of the various types of visual problems which the orthoptic technician handles and explains in detail what techniques are used for each type.

Orthoptic training is based on the theory that, when normal binocular vision is not achieved at the reflex level in infancy, it must be learned. The purpose of such training is to teach the individual how to control the existing muscle imbalance—so that he is a phoria rather than a tropia—and then increase his amplitude. One of the first steps is to teach the patient to recognize diplopia, and this is done in various ways according to the type of ocular problem.

The author states that all cases do not

lend themselves well to orthoptic treatment; factors to be considered are what the patient will gain by developing fusion habits and whether or not the benefits will be sufficient for the effort required. The four factors upon which orthoptic success depends are given as: (1) The patient must have reasonably good eyes that can straighten and function as a pair; (2) binocular vision must be fairly easy for the patient; (3) the patient must be able to recognize errors of binocular vision; (4) and the patient must want to use the eyes correctly.

The book does not attempt to cite any case histories to show what progress has been made through orthoptic training nor does it reveal if the results achieved can be expected to be of a permanent nature.

Beulah Cushman.

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The very readable Year Book unfolds its annual review of ophthalmology revealing "each new vista nobler than the last." The emphasis as usual is on the most practical and least controversial items. Discriminating selection combined with apt editorial comment reward the reader with a remarkable survey of what is good that is new, of what is new that is important, and the significance of it all. The numerous articles abstracted from state, foreign, and general journals is imposing and renders accessible important material that might otherwise escape perusal.

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Six papers discuss the retinopathy of premature birth and its differential diagnosis from persistent tunica vasculosa lentis and retinal dysplasia. Two articles emphasize the entity of pseudoglaucoma, where cupping and glaucomatous field defects are caused by some nutritional disturbance of the optic nerve—the ocular tension remaining normal.

In the 227 pages devoted to ophthalmology every subject receives adequate attention, including glaucoma (16 pages), surgery (23 pages), and therapy (20 pages), but the miscellaneous section (35 pages) is particularly fascinating. Among its many topics are allergy, collagen disease, irradiation, hyperlipemia, toxoplasmosis, and histoplasmosis. The index, unfortunately, is not as complete as it seems. For instance, the excellent article, "Use of electroretinography in measuring effect of vasodilation," page 95, has completely evaded the subject index, but could be located if the author's name (H. E. Henkes) was remembered. Otherwise the volume is *comme il faut*.

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tion in relation to the human eye. The book is divided into parts which gradually introduce to the reader a detailed technique of ocular optics and refraction.

After a short sketch of the history of ophthalmology, anatomy of the eye and the adnexa is presented in a concise form. The physiology of the eye is given more attention. Separate chapters deal with light adaptation, color vision, and peripheral vision. The history of the theories of color vision and the theories themselves, including the contribution to them of electroretinographic studies, are described in detail. Each chapter includes the methods of examination and description of various instruments for diagnostic purposes.

The optics of the eye are described with the minimum of mathematical formulas necessary to facilitate their understanding. Numerous examples are presented in the form of practical problems which are solved and which do not leave any doubt in the reader's mind. This method is used all through this book and should be of great help to those who are less familiar with physics or mathematics.

Separate chapters are given to accommodation, presbyopia, hyperopia, and astigmatism, as well as the methods of examination which include descriptions of different diagnostic instruments. Subjective and objective methods of refraction and examination of visual acuity are covered in three chapters. Only a very short chapter deals with the eye muscles.

The book ends with the description of spectacles and with the technique of fitting them. To acquaint the ophthalmologist with the work of an optician, the author presents many details on the optics and technique of making lenses. He describes the frames and even the optician's bench.

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Sylvan Brandon.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

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| 1. Anatomy, embryology, and comparative ophthalmology | 10. Crystalline lens |
| 2. General pathology, bacteriology, immunology | 11. Retina and vitreous |
| 3. Vegetative physiology, biochemistry, pharmacology, toxicology | 12. Optic nerve and chiasm |
| 4. Physiologic optics, refraction, color vision | 13. Neuro-ophthalmology |
| 5. Diagnosis and therapy | 14. Eyeball, orbit, sinuses |
| 6. Ocular motility | 15. Eyelids, lacrimal apparatus |
| 7. Conjunctiva, cornea, sclera | 16. Tumors |
| 8. Uvea, sympathetic disease, aqueous | 17. Injuries |
| 9. Glaucoma and ocular tension | 18. Systemic disease and parasites |
| | 19. Congenital deformities, heredity |
| | 20. Hygiene, sociology, education, and history |

8

UVEA, SYMPATHETIC DISEASE, AQUEOUS

Gasteiger, H. **Etiology of chronic uveitis.** *Klin. Monatsbl. f. Augenh.* 120:19-27, 1952.

Tuberculosis and focal infection are frequently mentioned as causes of chronic uveitis, yet certain proof of a tuberculous etiology is rare. Typical tuberculosis in any organ of the body must show caseation and the presence of tubercle bacilli. If we apply this criterion, the number of cases of ocular tuberculosis becomes very small. Likewise, focal infection should be considered a causative agent only when, after the removal of a local focus, a chronic uveitis disappears. Such cases also are rare. That every disease has one and only one etiologic agent has certainly not been proved. Probably there is never only one factor that brings about the active manifestation of a disease, but a multiplicity of factors that act together at a given time. Thus most cases of chronic uveitis must be considered as due to an allergic-hyperergic process in which a number of factors may act as provokers. The pathologic changes are

nonspecific ones, such as nodule formation, and point to a summation of stimuli which have been transmitted through the vasomotor nervous system. In this way old foci of infection may help to bring on a uveitis, or an allergy originating in a tuberculous focus may be activated by an infected tonsil or tooth. Such cases should not be called tuberculous; this term ought to be reserved for cases in which the bacilli can actually be demonstrated in the ocular tissue. (10 references)
B. T. Haessler.

Jaensch, P. A. **Diagnostic difficulties in metastatic carcinoma of the choroid.** *Klin. Monatsbl. f. Augenh.* 120:70-72, 1952.

A 50-year-old man, apparently in good health, had a circumscribed scleritis of the right eye. For two months his vision had been deteriorating. There was a retinal detachment. One month after he was first seen, the eye was enucleated because of glaucoma. A large, round tumor which had grown upward and nasally was found to have led to the retinal detachment. Because the tumor was not near the posterior pole, was not flat, and did not grow concentrically and because of the circum-

scribed scleritis, which was so obviously inflammatory, the correct diagnosis was not immediately made. The tumor proved to be the intraocular metastasis of a primary carcinoma of the left hilus. The ophthalmologist should realize that lung cancer and its metastases have certain peculiarities which differ from those described in the textbooks and in cases of inflammation of unknown origin, or when tumors are suspected he should always insist on an X-ray examination of the lung.

B. T. Haessler.

Kapusiński, W. J., Jr., and Drozdowska, S. **Diagnostic value of the Mantoux test in cases of inflammation of the mesenchymal tissue of the eye, treated by typhoid vaccine.** Arch. d'opt. 11:649-660. 1951.

The authors refer to the test, previously described by Kapusiński, for the differentiation of tuberculous uveitis from that due to focal infection. A small quantity of typhoid vaccine, 0.01 cc., is injected intravenously: in tuberculosis there is an increase in the uveitis and an irritation of the primary tuberculous focus; in focal infection the local ocular inflammation is reduced. In the present report the effect of this provocative test with typhoid vaccine on the Mantoux reaction is studied simultaneously with the study of its effect on the ocular disease. The authors argued that if the uveitis and the tuberculin reaction had a common denominator, the nonspecific shock test should produce an increase in the inflammatory signs in the skin as well as in the eye, and that if the uveitis were focal in origin the reaction of the eye would be independent of that of the skin. From a study of 75 cases they conclude that the results essentially substantiate their theory. In nine of their patients a tuberculous etiology was probable; the remainder, with the exception of a single syphilitic case, were in all probability due to focal infections.

The authors advocate their test for routine clinical use and conclude by referring to recent work on the relation of ACTH and cortisone to shock therapy.

P. Thygeson.

Otto, K.-H. **Iridocyclitis occurring after harvest fever.** Klin. Monatsbl. f. Augenh. 120:27-33, 1952.

Leptospira are spirochetes and were first investigated in Weil's disease where they bring on jaundice and other severe bodily changes. To date, 13 different types of leptospira have been described which cause benign disease without jaundice. Harvest fever, one of this group, is caused by *Leptospira grippo-typhosa*. The disease is endemic in many parts of Europe and may appear in epidemic form. A waterlogged soil, such as follows a flood, is essential for its development, and agricultural workers are the ones affected. Otto describes an epidemic he observed in the summer of 1948 to 1949. There was fever, general malaise, pain in the joints and circulatory disturbance. About half the patients showed an early conjunctivitis. Of the 15 patients, one had jaundice. The portal of entry is presumably the skin and the disease does not spread from person to person. The native population, possibly immunized by a similar epidemic 20 years before, was not as hard hit as migrant labor. Iridocyclitis was a late complication in eight patients (one patient had a papillitis also) and ran a chronic course. Three patients had acute recurrences with pain and ciliary injection and all had decreased vision and vitreous opacities. After treatment for two to 12 months all the eyes healed without functional damage. Treatment was palliative and nonspecific. In all these patients a positive serum reaction to leptospira had been obtained. Otto suggests that in cases of chronic iridocyclitis of undertermined origin the ophthalmolo-

gist consider the possibility of infection with leptospira. (6 references)

B. T. Haessler.

9

GLAUCOMA AND OCULAR TENSION

Kluyskens, Jean. **Congenital glaucoma.** Arch. d'opht. 11:574-577, 1951.

In an extensive, 240-page monograph, of which only an abstract is published here, the author advocates the use of the term "congenital glaucoma" to replace such other terms as "buphthalmos" and "hydrophthalmos." His first chapter contains an account of the history of the disease, in which the contributions of investigators from Ambroise Paré to Lagrange, Anderson, and Barkan are cited. The second chapter is devoted to personal observations on 24 cases, and the third chapter deals with the diagnosis of the disease. The anatomy of the iris angle and the gonioscopic picture are considered. The symptomatology, including enlargement of the globes, corneal opacification, photophobia and tearing, is described, with special comments on secondary alterations in the cornea such as hyposensitivity, rupture of Descemet's membrane, and edema of the cornea. The hereditary transmission is described as sometimes recessive and sometimes dominant.

In the fourth chapter, Kluyskens discusses the differential diagnosis of congenital glaucoma, with special reference to megalocornea. The fifth chapter is devoted to the histopathology of the disease and the sixth to its evolution and prognosis. Eventual blindness takes place in about 20 percent of cases. In the seventh chapter etiology is considered, and the various factors concerned in congenital alterations are analyzed. The eighth and final chapter is on treatment. The failure of miotics to be other than palliative is noted and early operation is advocated. The author prefers iridencleisis, and in

68 percent of the eyes his results have been satisfactory. Cyclodiathermy and goniotomy are discussed.

P. Thygeson.

Radnót, M. **The action of hormones in glaucoma.** Szemészet 2:114-115, 1951.

A man, 63 years old, had an attack of glaucoma after the administration of testosterone. If there is any suspicion of glaucoma, no testosterone preparations should be given. Gyula Lugossy.

10

CRYSTALLINE LENS

Cipriani, V., Enrique. **Discission-suction.** Rev. Peruana otorrinolaring. y oftal. 2:24-25, July, 1950-June, 1951.

The author does not consider discission of congenital cataract satisfactory because of slow absorption and the long period of reaction of the tissues of the eye. He describes a technique which he recommends for patients under 20 years of age, for traumatic cataracts of adults, and for liquefied hypermature cataracts. With the eye fixed, he introduces a 22 gauge, shortbeaded, sharp needle 2 mm. behind the limbus subconjunctively into the anterior chamber, scratches the lens in two or three different directions, then mobilizes the lens material into the anterior chamber and aspirates it with a syringe attached to the needle. This suction is repeated two or three times. He then fills the anterior chamber with air and withdraws the needle. Sulfathiazole or aureomycin ointment is applied, the eye left uncovered, and atropine is continued every two hours for two days. The operation is repeated at the end of two weeks if lens material still remains. Over 30 cases have been successfully treated.

Roberto Buxeda.

Cogan, D. G., Donaldson, D. D., and Reese, A. B. **Clinical and pathological characteristics of radiation cataract.**

A.M.A. Arch. Ophth. 47:55-70, Jan., 1952.

The clinical findings in 20 early cases of radiation cataract were reviewed and the histologic changes studied in cross sections from 27 cases of radiation cataract representing various stages of cataract formation. There were seven cases of cataract after exposure to X rays or gamma rays, 2 of cyclotron-induced cataract, 10 of cataract attributed to the ionizing radiations of the atomic bomb in Japan, and 1 of cataract resulting from an atomic explosion in this country. The findings were remarkably uniform in all cases. On ophthalmoscopic examination the initial opacity consisted of a dot, usually at the posterior pole of the lens, and as this increased to 1 to 2 mm. in diameter pepper-like granules and vacuoles developed about it. The main opacity then developed a relatively clear center, producing a doughnut-shaped pattern with a diameter of 3 to 4 mm. Granular opacities and vacuoles were found in the anterior subcapsular zone. These changes appeared to be stationary or were only slowly progressive over a period of several years. Later, progressive opacification of the cortex occurred, eventually forming a mature and nonspecific cataract. With slitlamp biomicroscopy, the initial opacities appeared granular and usually yellow.

The clinical features of radiation cataract in man are the doughnut-shaped configuration, as seen with the ophthalmoscope, and the sharply demarcated anterior boundary of the opacity and bivalve configuration of the opacity, as seen with the slitlamp biomicroscope. The histologic changes of radiation cataract consist of failure of the cells at the equator to differentiate into lens fibers, and early migration of cells beneath the posterior capsule toward the posterior pole. They are less type-specific than are the clinical signs. (9 figures, references)

R. W. Danielson.

Csillag, F. **Puncture of the capsule in intracapsular cataract extraction.** Szemészet 2:72-75, 1951.

For the removal of cataracts with a liquefied cortex, previous puncture of the capsule was recommended as early as 15 years ago. In animal experiments the resistance of the capsule to traction was greatest when puncture was done in the upper third. The capsule was grasped with the clamp at the bottom and the cataract was removed through tilting. Csillag has employed this procedure in the extraction of liquefied or swollen cataracts for 12 years with good results.

Gyula Lugossy.

Nónay, T. **Cataract operation in primary glaucoma.** Szemészet 2:107-113, 1951.

Sixty-nine patients with primary glaucoma were operated upon for senile cataract. The lens was removed while the intraocular pressure was less than 36 mm. Hg. The best results are obtained if the operation is performed with total iridectomy and preservation of the capsule after a proper preoperative treatment.

Gyula Lugossy.

von Sallmann, Ludwig, with the technical assistance of C. M. Munoz. **Abstract of paper: further efforts to influence X-ray cataract by chemical agents.** A.M.A. Arch. Ophth. 47:21-22, Jan., 1952.

von Sallmann and his co-workers last year reported, in a preliminary study, on the relation of cysteine treatment to X-ray damage of the rabbit's eye which had been exposed locally to a single dose of 1,500 r of penetrating X rays. There was evidence that epilation and X-ray cataract were partially prevented by the intravenous use of 2 gm. of cysteine before irradiation. These animals have been followed over periods of 12 to 16 months. Total cataract has developed in the con-

trol group in 12 of 14 animals. None of the cysteine-pretreated eyes showed a lenticular opacity dense enough to interfere with the visibility of fundus details. The complete paper will be published in the Transactions of the American Ophthalmological Society for 1951.

R. W. Danielson.

11

RETINA AND VITREOUS

Arkin, Wiktor. **Visibility of the yellow color in the abnormal macula with the red free light.** *Klinika Oczna* 21:66-69, 1951.

The yellow color in the macula of the fundus with early macular changes and edema was visible with the lighter red-free filter of the "Oculus" electric ophthalmoscope but not with a darker filter. The author feels that this is true because the tissue in the macula is less transparent than normal because of edema. Four case histories are presented.

Sylvan Brandon.

Bembridge, B. A., and Jackson, C. R. S. **Pathological examination of nine cases of retrolental fibroplasia.** *Brit. M. J.* 2:1484-1487, Dec. 22, 1951.

The retrolental membrane is formed of vascular connective tissue and is attached to the anterior part of the pars plana. The fibroblasts and the newly formed capillaries give the appearance of an inflammatory reaction. In nine eyes enucleated in the late stage of retrolental fibroplasia the retina was completely detached up to and past the pars plana. There was considerable folding of the retina and rosettes, hemorrhage, and exudates were present. Blood vessels of the retina may connect with the membrane and glial fingers may penetrate the membrane from a glial hyperplasia on the front of the retina. An exudate seen between the retinal pigment epithelium

and the other retinal layers contained many ghost cells. The signs of irritation in the anterior segment were not specific.

Irwin E. Gaynon.

Csapody, I. **Prophylactic operations on the retina.** *Szemészet* 2:68-72, 1951.

Tears and degenerated areas of the retina should be operated upon with penetrating diathermy before detachment develops. Early operation is safer than operation for detachment.

Gyula Lugossy.

Drew, A. L., and Magee, K. R. **Papilledema in the Guillain-Barré syndrome.** *Arch. Neurol. & Psychiat.* 66:744-751, Dec., 1951.

Only nine cases of papilledema have been reported in the Guillain-Barré syndrome which is a syndrome of radiculoneuritis with increased spinal fluid protein but without cellular response. A tenth patient, a man 38 years old, with the characteristic findings of this syndrome, and with marked papilledema, was studied through an illness lasting six months. Examination on admission revealed coarse lateral nystagmus, normal visual acuity and normal optic discs. Temporary paralysis of the right oculomotor nerve developed during the fourth week. During the sixth, painless bilateral papilledema of 3 D elevation and flame-like hemorrhages were seen around and on the discs. After two months the papilledema began to recede and in the sixth month there remained only a slight blurring of the disc margins. The authors believe that the mechanism of production of papilledema in the Guillain-Barré syndrome cannot at present be adequately explained. Claude L. LaRue.

Jervy, J. W. **Note on postoperative management of retinal detachment.** *A.M.A. Arch. Ophth.* 47:76-77, Jan., 1952.

In the three cases of retinal detachment described, the period of postoperative bed rest was considerably shortened, with no untoward effects. After surgical treatment of retinal detachment healing will occur quickly, as in any clean injury and will take place in spite of motion. The eye is not still in sleep or in closure, and cannot be splinted or stabilized. After the retina is back in place, it is doubtful whether any particular position is preferable.

The cases described indicate that the postoperative care of retinal detachment can, and should, be simplified, and that the eye tolerates this type of surgical procedure exceedingly well, as shown by the very slight reaction even when a second operation was performed after a short interval. R. W. Danielson.

Landesman, R., Douglas, R. G., and Snyder, S. S. **Retinal changes in toxemias of pregnancy; mild and severe hypertension, renal disease and diabetes mellitus.** *Am. J. Obst. & Gynec.* 63:16-27, Jan., 1952.

The retinal changes in acute toxemia are less advanced than in hypertensive and renal disease because of the lack of pre-existing arteriolar disease. In severe hypertension the state of the retinal arterioles is important in prognosis, whereas in mild hypertension early retinal changes are of little prognostic value. The need for the interruption of pregnancy depends on the degree of retinal arteriolar damage in severe hypertension. The presence of retinal hemorrhages, exudates, or papilledema associated with hypertension, are indications for prompt interruption regardless of the duration of gestation. In chronic renal disease with normal blood pressure and normal retinal vessels a living infant is probable; the chance for a living infant decreases as the severity of retinovascular changes increases. The prognosis for the fetus is

worse when retinal vascular changes are associated with diabetes mellitus and toxemia than with toxemia alone. When grade II retinal arteriolar changes are present in a diabetic patient the fetus will die unless there is early intervention. A woman with diabetic retinopathy should be advised against pregnancy. (7 figures, 7 references) Bennett W. Muir.

Lanman, J. T., Guy, L. P., and Dancis, J. **Adrenocorticotrophic hormone in the therapy of retrolental fibroplasia.** *Pediatrics* 9:27-31, Jan., 1952.

Five premature infants thought to be developing retrolental fibroplasia were treated early and vigorously with ACTH. Treatment was begun between the 7th and the 37th day of life and was given for 30 to 60 days. The usual dose was 20 to 40 mg. per day. One patient died during therapy and in the four remaining patients retrolental fibroplasia progressed to cicatrix formation behind the lens. The therapy was totally ineffective. (5 figures, references) Bennett W. Muir.

Ludvig, I., and Németh, B. **The visual field in operated cases of retinal detachment.** *Szemészet* 2:95-98, 1951.

On examining the visual field of 56 patients operated upon for retinal detachment, the authors found that successful operation was followed by an increase in the visual field for objects and colors within three weeks, unless complicated by severe atrophy of the choroid and degenerative changes. If color vision does not return, it is a sign of incomplete cure or of recurrence. Gyula Lugossy.

Palich-Szántó, Olga. **Retinal cysts.** *Ophthalmologica* 122:283-294, Nov., 1951.

Two cases of isolated cysts of the retina in the macular region are described and interpreted as developmental anomalies related to folding of the retina.

Peter C. Kronfeld.

Rieger, H. **A further report on cases of central external exudative retinitis presumably caused by an acquired, adult toxoplasmosis.** *Klin. Monatsbl. f. Augenh.* 120:33-50, 1952.

In a recent issue of the *Klin. Monatsbl. f. Augenh.* Rieger reported four cases of retinitis due to adult toxoplasmosis. A titer curve, taken over a period of ten months, definitely established the diagnosis in one case and helps to make this diagnosis all the more probable in the other, clinically similar cases. In this article he discusses his previous report and adds ten further cases. They are classified as early, late, healed, but with relapse, and completely healed. The late severe cases may show changes similar to those seen in retinitis circinata; in one case described there were cysts of the retina, in another peripapillary edema. Involvement of the retinal vessels occurred several times and occasionally the periphery of the fundus was affected so that choroiditis was simulated. Paralysis of the eye muscles may be an important symptom. In about half the patients one eye only was involved. The Sabin-Feldman test can be considered specific for *Toxoplasma gondii*, although Rieger does not believe that a negative test rules out infestation, especially if the infection occurred long ago. The results of the tests are reported in tabular form. The source of infection could often be traced to dogs, rats or rabbits. Treatment consisted of large doses of Supronal, continued for months after the symptoms subsided. The fact that central external exudative retinitis is a specific disease should help distinguish between latent and manifest toxoplasmosis and aid in checking the spreading menace of this disease. (2 figures, 3 tables, 11 references)

B. T. Haessler.

Sobański, Janusz. **Venous pulse of the retina.** *Klinika Oczna* 21:8-18, 1951.

The author believes that the venous pulse is similar to the arterial pulse and is the result of passage of the pulse wave through the arteries and the capillaries into the veins. A venous pulse becomes visible when the intraocular pressure is higher than the pressure of the blood in the retinal veins at the time of the diastole of the heart. It is slightly retarded in time by comparison with the arterial pulse. The mechanism of the pulse is different when the venous pressure is high and reaches the median pressure of the retinal artery. The vein is compressed at the time of dilation of the arteries, as was described by Bailliar. The author was able to take a motion picture of the venous pulse and presented the film at the Ophthalmological meeting in Cracow in September, 1949. Sylvan Brandon.

Weiman, C. G., McDowell, F. H., and Plum, F. **Papilledema in poliomyelitis.** *Arch. Neurol. & Psychiat.* 66:722-727, Dec., 1951.

Of 106 patients with acute poliomyelitis, five, with moderate to severe quadriplegia, developed papilledema, with blurred vision and diplopia, from 11 to 48 days after the onset of illness, and with an average duration of 60 days. Three had systemic arterial hypertension and required a respirator. Spinal fluid pressure was elevated; there was headache, fever for five to ten days and muscular paralysis with typical anterior horn cell distribution. Visual fields and visual acuity were normal. The papilledema was presumably part of a generalized edema of the central nervous system. Claude L. LaRue.

13

NEURO-OPHTHALMOLOGY

Arkin, Wiktor. **A rare case of abortive migrainous ophthalmoplegia.** *Klinika Oczna* 21:70-72, 1951.

Four cases of temporary paralysis of

the pupil of one eye in patients with mi-grain are described. The pupil was dilated and there were no other ophthalmological symptoms. Sylvan Brandon.

Booth, Carl B. **Does nystagmus occur in lesions of the cervical cord?** Arch. Neurol. & Psychiat. 67:69-71, Jan., 1952.

It is important to make a differential diagnosis between supracervical and cervical lesions, especially those due to herniated cervical disc. The frequency of nystagmus in cervical lesions was determined, and an extensive review of the literature is given. Explanation of the mechanisms by which lesions in the cervical cord produce nystagmus are largely speculative. An interruption in the pathway of the medial longitudinal fasciculus is possible but unlikely. Traction on the medulla, with secondary involvement of the vestibular pathways, may be present in extramedullary cord lesions. The study indicates that nystagmus is uncommon in connection with lesions of the spinal cord of the cervical region. In the differential diagnosis of cervical and supracervical lesions nystagmus points strongly to a supracervical disorder rather than to a cervical one. Claude L. LaRue.

Chang, Hsiang-Tung. **Cortical response to stimulation of lateral geniculate body and the potentiation thereof by continuous illumination of retina.** J. Neurophysiol. 15: 5-26, Jan., 1952.

During experiments on stimulation of the geniculate body of cats it was accidentally discovered that exposure of the retinas simultaneously to light caused a potentiation of the stimulus. The pattern of cortical response to stimulation of the lateral geniculate body has been found to be the same as that to optic nerve stimulation, except that the over-all latency was shorter in the former than in the latter, indicating a monosynaptic relationship in the lateral geniculate body between

the optic nerve and the radiation fibers. Continuous illumination of the retina potentiates the cortical response obtained by stimulating the lateral geniculate body. The potentiation develops in five seconds and is sustained as long as the illumination is continued with waxing and waning at a frequency of six cycles per minute. Spontaneous electrical waves of the cortex appear to be greatly suppressed. The site of the potentiation is in the lateral geniculate body. (15 figures)

H. C. Weinberg.

Henderson, J. W., and Crosby, E. C. **An experimental study of optokinetic responses.** A.M.A. Arch. Ophth. 47:43-54, Jan., 1952.

Intact preoccipital and occipital eye fields are essential for normal optokinetic responses. If both these fields are ablated bilaterally, such responses are abolished. If the appropriate portions of the preoccipital and the occipital eye fields are destroyed unilaterally, optokinetic responses are not elicited on rotation of the drum away from the side of the injury. If the portion of one preoccipital eye field functionally related to conjugate horizontal deviation of the eyes is destroyed, the homolateral occipital eye field may still produce an optokinetic response in the expected direction. Bilateral destruction of considerable portions of the frontal eye fields, including those regions related to horizontal deviation of the eyes, makes possible maximal optokinetic responses in the horizontal, and probably in other, planes. (3 figures, references)

R. W. Danielson.

Lowenstein, O., and Lowenfield, I. E. **Disintegration of central autonomic regulation during fatigue and its reintegration by psychosensory controlling mechanisms: I Disintegration. Pupillographic studies.** J. Nerv. & Ment. Dis. 115:1-21, Jan., 1952.

All fatigue manifested in pupillary reflex activity is central in origin. The sympathetic centers become fatigued before the para-sympathetic centers, and the cortical before the subcortical. Pupillograms and differential analyses of the normal reflex to light in man, monkey, and cat are presented. (13 figures, 18 references)

Bennett W. Muir.

Pryor, William D. **The pupillary changes associated with diabetic neuropathy.** North Carolina M. J. 12:605-607, Dec., 1951.

A variety of changes in pupillary size and reactions may occur in diabetic neuropathy. Typical Argyll Robertson pupils may be seen in the absence of any evidence of neurosyphilis. An Argyll Robertson pupil with loss of knee and ankle jerks may occur in diabetic neuropathy.

Irwin E. Gaynon.

14

EYEBALL, ORBIT, SINUSES

Pagani, Mario. **Tumors and cysts of the orbit.** Rassegna ital. d'ottal. 20:402-420, Nov.-Dec., 1951.

The anatomic schema of the orbital structures and the new growths occurring there, as proposed by Benedict, is illustrated and carefully described by the writer. He prefers certain changes in the nomenclature as presented by Offret. Descriptions of many tumors and cysts of the orbit and the operative procedures employed in their treatment are given. (20 figures)

Eugene M. Blake.

Wilczek, Marian. **Posterior encephalocele of the orbit.** Klinika Oczna 21:41-49, 1951.

The most frequent congenital condition causing loss of bone tissue in the posterior segment of the orbit is the encephalocele. The symptoms, location and the structure of the encephalocele

are described and two cases are presented. In both the opening was in the area of the large and the small sphenoidal wing, which were missing. One likewise had a neurinomatosis of von Recklinghausen.

Sylvan Brandon.

15

EYELIDS, LACRIMAL APPARATUS

Allen, James H. **Lids, lacrimal apparatus, and conjunctiva. Review of the recent literature.** A.M.A. Arch. Ophth. 47:87-112, Jan., 1952.

This excellent annual review should be read in its entirety. (References)

R. W. Danielson.

Friberg, Torsten. **The role of the lacrimal sac and of the caruncle in the elimination of tears.** Ophthalmologica 122:193-206, Oct., 1951.

In previous publications (Zeitschr. f. Augenheilkunde, vols. 37, 39 and 67) the author arrived at a concept of the mechanism of tear conduction in which the lacrimal sac played a significant part. The manometric studies of Rosengren and Kugelberg (Klin. Monatsbl. f. Augenh. 95, 1935) proved the importance of the canaliculi but seemed to speak against any participation of the tearsac in the process of tear elimination. In the paper under review Friberg reviews the data of Rosengren and Kugelberg and a number of pertinent clinical observations and finally reaffirms his original concept according to which the movable parts of the channels of elimination function as a combined pressure and suction pump. In the starting position of open palpebral fissure the tone of the orbicularis and the elasticity of the surrounding tissues tend to keep the canaliculi and the sac open. This results in negative pressure within the elimination channels and a slow aspiration of tears from the lacrimal lake. This physiological process is interfered with by

senile relaxation of the orbicularis or slight obstructions near the puncta. During the blinking movement the canaliculi and the sac are compressed and their contents forced toward the nose. Regurgitation into the conjunctival sac is prevented by a complex mechanism the most important part of which is probably firmer apposition between punctum and the tissues behind it. In cases of unusually large outflow channels, gravity alone may cause a flow of tears into the nose. The caruncle seems to play a passive part in that it transmits the pressure of the orbicularis to the canaliculi and the sac.

Peter C. Kronfeld.

Garzino, Alessandro. **The histology of the lacrymal sac at various ages.** *Rassegna ital. d'ottal.* 20:343-381, Nov.-Dec., 1951.

Many lacrimal sacs were removed at all ages from birth into advanced years and the histological examinations are summarized. The sac of the new-born and in youth has a normal histological appearance. In the adult, one finds evidences of attenuated chronic inflammatory changes which tend towards cicatrization and sclerosis. Epiphora is more frequent in old people because of a tendency to stenosis at the outlets of the duct and from compression by lymphatic follicles, and chronic dacryocystitis is more frequent. There is a marked similarity in the histologic aspect of the two sacs in an individual. Tumor-like cells are sometimes seen and form adenomatous and cystic areas. In the walls of the sac one frequently sees glands of the serous type, especially in the young. (31 figures, 29 references)

Eugene M. Blake.

Grönvall, Herman. **Statistics relating to the occurrence and location of 1,693 chalazia.** *Acta ophth.* 29:329-338, 1951.

A statistical analysis of 1,693 cases shows that chalazia are more frequent in

boys under ten, and in girls between ten and twenty years of age. There is a greater tendency for chalazia to involve the left eye. There is no demonstrable difference in the involvement of the upper and lower lids. The temporal half of the lid is more often involved in men, the nasal in women. In men, the upper temporal and the lower nasal quadrants are the most frequent sites of chalazia, the upper nasal less frequent. In women the lower nasal quadrant is most often affected. (4 tables)

Ray K. Daily.

Hasegawa, Bungo. **Etiology of angular and marginal blepharitis, particularly with regard to *Micrococcus conjunctivae* Mitsui-Hinokuma.** *Acta Soc. Ophth. Japan* 56:9-14, Jan., 1952.

The author re-examined the etiological role of *Micrococcus conjunctivae*, first described by Mitsui and Hinokuma (*Am. J. Ophth.* 34, Sept., 1951) in angular and marginal blepharitis and confirmed their findings in most respects. He examined 35 cases of angular and marginal blepharitis and found the micrococcus in all. Five strains were isolated and identified. Inoculation with the micrococcus into two human eyes resulted in an onset of marginal blepharitis. Vitamin B₆ was effective in the treatment of the angular form but less effective in the marginal form. The author concludes that *Morax-Axenfeld's* bacillus and the micrococcus may be symbiotic and coöperative, but the former is the chief cause of angular blepharitis and the latter of marginal blepharitis.

Yukihiko Mitsui.

Markovitch, A. **Classification of trachoma.** *Arch. d'opht.* 11:571-573, 1951.

Markovitch states that there are only two periods in the evolution of trachoma, the period of progression and the period of regression. He has devised a new classification in which the stage of progression is divided into incipient (P₁)

and florid (P_2) phases, and the stage of regression is divided into the hypertrophic-cicatricial (R_1) phase and the cicatricial (R_2) phase. He describes in detail the clinical characteristics of these four phases. P. Thygeson.

Nagy, F. **Restitution of tear drainage after extirpation of the lacrymal sac.** Szemészet 2:98-101, 1951.

Three cases of restitution of tear drainage after extirpation of the lacrymal sac are reported. In cases characterized by the formation of a pseudocyst, dacryocystorhinostomy is the proper procedure. In other cases canaliculo-rhinostomy is more adequate. In cases complicated by fistula, filling with black thread should be done during operation.

Gyula Lugossy.

Pavišić, Zvonimir. **Plastic trichiasis operation.** Ophthalmologica 122:50-52, July, 1951.

For recurrent entropion and trichiasis due to trachoma the author recommends the transplantation of an approximately rectangular piece of ear cartilage (with the overlying skin) into the intramarginally split lid. Peter C. Kronfeld.

Sjögren, H., and Kronning, E. **Keratoconjunctivitis sicca after partial extirpation of the palpebral lacrimal gland.** Acta ophth. 29:355-360, 1951.

Keratoconjunctivitis sicca sometimes follows extirpation of the palpebral lacrimal gland, with obliteration of the lacrimal ducts, for epiphora after dacryocystectomy. In the case reported, a 16-year-old woman had had an unsuccessful Toti-Kuhnt operation for lacrimal stenosis, followed five years later by partial excision of the palpebral lacrimal gland for annoying epiphora. Three years later she was found to have symptoms of keratoconjunctivitis sicca. Lacrimal secretion as determined by the Schirmer test was not completely lacking, but was considerably

reduced. The diagnosis was confirmed by biopsies from the temporal and nasal portions of the bulbar conjunctiva. It is interesting that keratoconjunctivitis sicca developed in spite of the complete stenosis of the lacrimal duct. The authors agree with Spaeth in the emphatic condemnation of excision of the lacrimal glands for epiphora. Ray K. Daily.

Van Manen, J. G. **A special lid plate for Ewing's entropion operation.** Ophthalmologica 121:259-263, May, 1951.

Two instruments described by Henry and Trabut (Am. J. Ophth. 33:1011, 1950) were combined into a special lid plate that serves well to steady the lid during the entropion and trichiasis operations of the Ewing type which are widely practiced in the Dutch East Indies for the relief of the effects of trachoma.

Peter C. Kronfeld.

Veirs, Everett R. **Nonsurgical repair of strictures of the lacrimal drainage system.** A.M.A. Arch. Ophth. 47:71-75, Jan., 1952.

The treatment of patients with partial stenosis of the lower lacrimal canaliculus by the use of nylon rods or plastic tubing is simple and satisfactory. The nylon rod described by the author can be inserted into an injured canaliculus immediately after an injury, at the time the wound is sutured. This is far preferable to trying to make a new channel through scar tissue later. The polyethylene tubing, when it is passed through the lower canaliculus, tear sac, and nasolacrimal duct, using the thin-walled, blunted needle, will cure a large percentage of cases of dacryocystitis. (3 figures, references) R. W. Danielson.

16

TUMORS

Auricchio, G. **Metabolism of ocular tumors.** Boll. d'ocul. 30:393-403, July, 1951.

The oxygen consumption of seven choroidal melanomas and four retinal gliomas was measured with Warburg's manometric method, and aerobic and anaerobic glycolysis was studied. The results are summarized in two tables showing, in both types of tumors, an elevated aerobic glycolysis and a constantly positive excess fermentation (factor U). Respiration in all experiments was higher than one. Similar findings in other tumors suggest that the ocular tumors undergo not only a morphologic but also a metabolic change as compared to their matrix. Histologically as well as chemically, the properties of the original tissue seem to be altered. High glycolysis and low respiration are not explained by the malignancy of the anaplastic tissue but more probably by its decreased vitality. K. W. Ascher.

Seuss, A., and Stutz, E. **X-ray treatment of retinoblastoma.** *Strahlentherapie* 85:589-593, 1951.

In unilateral retinoblastoma, operation is of course the treatment of choice. When the disease is bilateral, X ray or radium sometimes brings about a permanent cure. However, only those cases are reported in which treatment has been successful, many more are seen and treated without success, and therefore are not reported in the literature. About a dozen cases are known in which spontaneous regression took place. One such case is here described. At three-and-a-half years of age one eye had been enucleated and the diagnoses of bilateral retinoblastoma had been definitely established. Enucleation of the second eye was refused. During the following eight years the disease gradually regressed, the vision is unimpaired and the general health of the child is good. May not apparent cures after X-ray or radium treatment actually be spontaneous remissions? Excellent results have been reported with radium by English workers and these should not be overlooked when it is necessary to decide on

treatment of a second diseased eye. Healing by radium therapy far exceeds spontaneous healing and should be carried out whenever possible.

B. T. Haessler.

Stallard, H. B. **Surgery of malignant melanoma of the iris.** *Brit. J. Ophth.* 35: 774-783, Dec., 1951.

Malignant melanomas of the iris are usually of the spindle cell type and contain much argentophil reticulin. Clinically there is the nodular type, the flat, and the diffuse or "ring" sarcoma. The cornea and iris angle should be carefully examined for signs of extension of the growth. Enucleation of the eye when the tumor is limited to the iris is not justified. In the excision of the lesion a conjunctival flap is made by cutting it from the limbus for one-half the circumference. An ab externo incision is made and the iris is cut outside two iris forceps which are used to grasp on either side of the mass. The wound is closed by a preplaced corneoscleral suture brought out through the conjunctiva and tied. Sutures at the ends of the flap pull the conjunctiva down over the wound, and completely cover it. Five cases of successful removal are reported, well illustrated with photographs and photomicrographs. In one case the tumor, which has extended to the iris root, was treated with surface diathermy. The eye was subsequently enucleated and careful study revealed no histological evidence of the malignant melanoma. One tumor appeared to be unaffected by unscreened radium given four months before excision. (10 figures, 16 references)

Orwyn H. Ellis.

17

INJURIES

Alvis, E. B. **Eye care in battalion aid stations.** *J. Missouri M.A.* 48:958-960, Dec., 1951.

Six percent of battle casualties involve the eye and almost half of the men are unable to return to combat duty. Methods of treatment for lost glasses, eye diseases, burns, wounds near the eye and adnexa, and penetrating and lacerating wounds of the globe are suggested. At least one of the antiseptic drugs, some combination of antiseptic and anesthetic and 1-percent atropine should be available for immediate use in the forward areas.

Irwin E. Gaynon.

Corrado, Antonio. Laceration of inferior rectus muscle by cow's horn. *Rassegna ital. d'ottal.* 20:185-200, July-Aug., 1951.

The left eye of a 50-year-old farmer was struck by the horn of a cow, with resulting complete laceration of the upper lid, tear of the bulbar conjunctiva and severing the inferior rectus muscle. Rupture of the globe was suspected as the eye was soft and the vitreous full of blood. Suture of the eyelid, and conjunctiva and reattachment of the inferior rectus resulted in good cosmetic appearance, normal vision and but slight esophoria and hyperphoria. This is the forty-sixth reported case of laceration of the inferior rectus. (3 figures, 54 references) Eugene M. Blake.

Hull, Forrest E. Management of eye casualties in the Far East command during the Korean conflict. A preliminary report. *Tr. Am. Acad. Ophth.* pp. 885-891, Nov.-Dec., 1951.

Approximately 3,200 patients with eye injuries or eye diseases were treated in the Tokyo Army Hospital from July, 1950, to June, 1951, or about 12 percent of the total admissions. During that period 126 enucleations were performed. About 50 percent of head injuries had associated eye damage. Most cases of eye injury are seen within 24 hours. The routine emergency treatment included the use of penicillin, sulphadiazine or sodium acetamide

instillation, and sulphacetamide ointment, and, in cases of uveal and corneal injury, atropine. Removal was attempted in 77 of 80 cases of intraocular foreign body, successfully in 51, of which 31 were magnetic. The Lancaster hand magnet and the Bermann localizer were of great value and a modified Sweet localization was employed. No attempt was usually made to remove small nonmagnetic foreign bodies from the eye. The removal of foreign bodies within 24 hours after injury is considered an important factor in recovery. Macular holes were frequently associated with contused wounds and subluxated lenses. The routine treatment of burns, due most often to napalim, battery acid, lime and phosphorus included the use of local anesthesia, irrigation and 5-percent sulphhydryl solution in oil or gel. Among the antibiotics employed were penicillin, aureomycin, streptomycin, chloromycetin, and terramycin, none of which apparently had any specific advantage. Sulphadiazine was considered the most effective of the sulpha drugs. Chas. A. Bahn.

Knapp, Arthur Alexander. Simple removal of ocular foreign bodies, a manual method. *J.A.M.A.* 148:119, Jan. 12, 1952.

An eye containing a nonmagnetic foreign body is in great danger and sympathetic ophthalmia must be guarded against. Extraction of the foreign body is difficult, is seldom successful, and may be followed by blindness, and atrophy, necessitating enucleation. The case of a young boy is reported; X-ray examination of the eye showed a BB shot in the vitreous. No wound of entrance was found because of edema and hemorrhage into the anterior segment. In exposing the sclera, traction on the lids with pressure on the posterior aspect of globe suddenly forced the shot out below the limbus through the wound of entrance. The eye recovered and there was no sympathetic ophthalmia. Keeping the

head in a position to promote the pull of gravity toward the wound, followed later by gentle manual expression, will often save the eye. This method might also be used with magnetic foreign bodies and can be performed by any physician without special training in ophthalmology.

Claude L. LaRue.

Kuhn, Hedwig S. **Industrial eye injuries.** Tr. Am. Acad. Ophth. pp. 891-896, Nov.-Dec., 1951.

Through the enforcement of an effective eye protective program ninety percent of industrial eye injuries could be prevented. Such a program primarily involves: 1. a survey of the specific eye hazards involved; 2. the adherence to a predetermined plan; 3. the prescription, delivery, and maintenance, of protective-refractive glasses adapted to the industrial needs of each individual and maintained by a mobile or maintenance station; 4. the use of only government-approved optical and safety merchandise; 5. the ocular examination of all employees, old and new; 6. the furnishing and maintenance of necessary safety equipment, such as machine guards; 7. prompt and efficient care of injured eyes.

Chas. A. Bahn.

Küster, Albert. **Injury to the eye from thioglycolic acid during a "cold wave" permanent.** Klin. Monatsbl. f. Augenh. 119:616-618, 1951.

Thioglycolic acid, an ingredient of "cold wave" preparations, liberates ammonia and may seriously injure the eye. A case of injury to the cornea which remained unchanged after eight months and was uninfluenced by any treatment is reported. The author instilled a similar solution into rabbits' eyes and brought about clouding of the cornea which progressed from the periphery deep into the parenchyma.

B. T. Haessler.

Nemec, Hans. **A new treatment of caus-**

tic burns of the eye brought on by indelible pencils. Klin. Monatsbl. f. Augenh. 119:540-542, 1951.

Basic aniline dyes, specifically methyl violet, are used in indelible pencils and may cause injuries to the eye, such as conjunctival necrosis and ulcers and may even penetrate the sclera and bring on dense scars. Subconjunctival injections of vitamin C have been very successful in counteracting the discoloration and inflammation brought on by such injuries. Vitamin C is likewise applied locally and intravenously.

B. T. Haessler.

Schneider, R. C., and Henderson, J. W. **Penetrating orbital wound with intracranial complications.** A.M.A. Arch. Ophth. 47:81-85, Jan., 1952.

The authors report a case of penetrating wound of the orbit with communication between the carotid artery and the cavernous sinus. Extensive intracranial damage resulted, even though the original wound was slight and immediate ophthalmological and neurological changes were absent. The neurological pattern was confusing and was clarified only at autopsy. (3 figures)

R. W. Danielson.

Sédan, J., and Halbron, P. **Ocular injuries from the spines of sea-urchins.** Ann. d'ocul. 184:1015-1021, Nov., 1951.

Sea urchins are small, round, spiny animals not uncommon along the Mediterranean shore. Their numberless spines are extremely sharp and fragile. When striking the eye they penetrate quite deeply, are difficult to remove, frequently are toxic and may cause localized necrosis. Children often play with sea urchins and throw them about like balls. Three cases of corneal or scleral perforating wounds are reported, two in children and one in an adult. In one case enucleation had to be done because of a secondary keratouveitis and global atrophy. The other two

patients recovered with little loss of vision. In one patient a partial trephine operation was necessary to remove a penetrating spine and in another a spine had to be removed from the anterior chamber.

Chas. A. Bahn.

18

SYSTEMIC DISEASE AND PARASITES

Chan, Eugene. **The ophthalmoscopic findings in a case of Banti's syndrome.** *Ophthalmologica* 122:249-252, Oct., 1951.

In an apparently typical case of Banti's syndrome with moderately severe anemia, the author found a peculiar brownish tinge of the eyeground, a salt-and-pepper appearance of the periphery, slightly narrowed arterioles and a pale disc.

Peter C. Kronfeld.

Dana, G. W., Eversole, S. L., and Zubrod, C. G. **Hyperglycemia and its relationship to diabetic retinitis and glomerular nodules: preliminary report.** *Bull. Johns Hopkins Hosp.* 90:98-99, Jan., 1952.

An analysis of 190 patients with diabetes mellitus, autopsied at the hospital, showed that patients with capillary aneurysms of the retina, glomerular nodules, and hyperglycemia without acidosis have a specific metabolic defect different in mechanism from simple insulin deficiency. In 51 patients with glomerular nodules in the kidney, 45 had had aneurysms of the retinal capillaries clinically. Retinal aneurysms occurred rarely without glomerular nodules. (3 references)

Bennett W. Muir.

Djacos, C., and Joannidès, T. **Sturge-Weber-Krabbe disease.** *Ann. d'ocul.* 184:994-1014, Nov., 1951.

This degenerative syndrome is primarily a cerebral and cutaneous angiomatosis. Its ocular manifestations include an-

giomata in practically every part of the eye, orbit and brain, alone or in combination with glaucoma. The basic lesion is apparently a genetic predisposition to impaired venous permeability with resulting dilatation and metaplasia. Ocular angiomas may be monolateral or bilateral and frequently follow the course of the fifth nerve. The associated glaucoma is believed to be due to increased production of aqueous; the anterior chamber angle is usually open. The author reports three cases in detail to illustrate the principles involved.

Chas. A. Bahn.

François, Jules. **When should we think of toxoplasmosis?** *Ann. d'ocul.* 184:1022-1029, Nov., 1951.

Ocular toxoplasmosis is frequent and is often confused with developmental ocular malformations. In more than 90 percent of the cases reported, the infection occurred before birth and was binocular. The disease is transmitted through the mother who may or may not have active evidence of toxoplasmosis. Marked differences in the severity of the disease in the two eyes are frequent. The ocular manifestations are part of an inflammatory process which involves the meso- and neuroblastic tissues in different parts of the body. The earlier the disease, the more severe the symptoms. In both the acute and chronic congenital forms, the macular area alone is involved in one third of the patients, the macular and peripheral areas in a third, and the periphery alone in a third. Fundus lesions tend to be more diffuse in the last group. The less frequent ocular manifestations include: microphthalmia in 25 percent, secondary to anterior or posterior uveitis; noninflammatory optic atrophy in 20 percent, usually secondary to cerebral involvement; and other complications such as retinal falciform folds and motor abnormalities, including nystagmus and strabismus. The diagnosis can be made in 90 percent of potential cases from the

symptoms, cerebral calcification and the dye test of Sabine and Feldman.

Chas. A. Bahn.

François, Jules. **Unilateral hypertonicity of the elevator of the lid in Basedow's syndrome.** *Acta ophth.* 29:305-327, 1951.

The retraction of the upper lid in Basedow's disease is usually bilateral, but even an isolated unilateral retraction should suggest hyperthyroidism. The author reports seven cases of unilateral retraction of the upper lid, caused by a disturbance in thyroid metabolism and points out that this condition is not as rare as is generally believed. Unilateral exophthalmos may be regarded as definitely hyperthyroid in origin if it is associated with retraction of the upper lid; three such cases are briefly reported. In one case of bilateral exophthalmos the retraction of the upper lid was unilateral. Theories of the pathogenesis of unilateral retraction of the lid are critically reviewed, and the author concludes that the retraction of the upper lid in Basedow's disease is due to an increased tone of the striated muscle of the lid elevator, similar to that observed in Parkinson's disease and in diseases of the extrapyramidal tract or hypothalamic centers. The hypertonicity is due to a motor disturbance in the diencephalo-mesencephalic centers, which is caused by excessive thyrotropic hormone, and is the result of pituitary hyperactivity. (12 figures, references) Ray K. Daily.

Friedmann, Martin. **Thelaziasis of the conjunctiva.** *Ophthalmologica* 122:252-254, Oct., 1951.

As an addition to a paper reviewed in *Am. J. Ophth.* 33:328, 1950, the author reports another case of thelaziasis of the conjunctiva which occurred in an entomologist engaged in entomological survey work in San Diego County, California. The author never saw the patient but

made the diagnosis from the clinical history and the microscopic appearance of the worm that worked its way through the conjunctiva. Peter C. Kronfeld.

Löhr, K. **The prognostic significance of the fundus findings in tuberculous meningitis when treated with streptomycin.** *Klin. Monatsbl. f. Augenh.* 119:533-540, 1951.

The mortality of tuberculous meningitis has fallen from 99 percent to about 50 percent since treatment with streptomycin was begun, and the disease may now be of many years' duration. Löhr examined the fundus, under atropine, in 55 cases of tuberculous meningitis at 8 to 10-day intervals. There were changes in the fundus in 83 percent of all cases observed, most of them caused directly by the increased cerebral pressure. These consisted of peripapillary edema and venous stasis, and, later, choked disc up to 4 or 5D, without materially influencing vision.

Five patterns can be distinguished in the clinical courses of tuberculous meningitis: 1. acute meningitis, which rapidly ends fatally and is uninfluenced by streptomycin, 2. gradual healing within 60 days, 3. after an acute phase, the disease gradually turns into type 2, 4. types 1 and 2 begin concurrently so that a distinction between them is no longer possible, 5. in any pattern acute recurrences with toxic manifestations may occur. The ophthalmoscopic picture accurately parallels these phases. In the encephalotoxic phase, with peripapillary edema and choked disc, prognosis is relatively favorable. When encephalopathy has developed, atrophic processes, from temporal pallor of the papilla up to optic atrophy are seen. Prognosis is poor, and severe defects remain if the patient lives. If tuberculous disease of the blood vessels can be seen, prognosis is bad, not only as to vision, but also as to life.

With streptomycin treatment, 51 percent of children recovered, 14 percent re-

tained severe defects, such as complete blindness or deafness and internal hydrocephalus; 4 percent showed mild residua, such as temporal pallor of the papilla, deafness in one ear, and some psychic changes. Only 12 children (22 percent) were completely healed. (2 figures, 3 tables)

B. T. Haessler.

Ludwig A., and Vurdelja, N. **Eye findings in masked encephalitis.** *Ophthalmologica* 122:295-307, Nov., 1951.

The masked or larvate encephalitis referred to by the authors leaves in its wake a neurasthenia-like complex of symptoms of which the Yugoslav neurologist Vujić and the Italian neurologist Calligaris have made special studies. Ophthalmologically these cases are characterized by a low ocular tension (12 to 17 mm. Hg Schiøtz), a strikingly deep physiologic excavation and marked venous pulsation within this excavation. A correlation between the neurological disorder and the eye findings is attempted. (References)

Peter C. Kronfeld.

Madrid de Obeid, Ilda. **Ocular Tuberculosis.** *Rev. Fac. de Ciencias med.* 9: 305-347, May-June, 1951.

A description of tuberculous infection in general is given and the concepts of tuberculous allergy and immunity and their interrelation are discussed. Ocular tuberculosis is considered in its relation to the pulmonary tuberculosis and the experimental work of Woods on immunity and allergy in the ocular disease is described. A description of the diagnostic methods and a chapter on treatment which includes the technique of tuberculin therapy, auric therapy and methylic antigen follow. In a second part, the condition of dacryoadenitis is described and a case is reported. Treatment consisted of streptomycin together with methylic antigen therapy. Surgical treatment is not always the only one indicated

and the value of antibiotics in this connection is emphasized. (5 figures, 12 references)

A. Arruga.

Olmer, J., Poursines, Y., and Farnarier, G. **The retinal manifestations of the acute leukemias.** *Semaine d. hôp. Paris* 27:3783-3798, Dec. 22, 1951.

Of 26 patients with acute leukemia studied, three had normal eyegrounds except for the general anemic aspect of fundus and disc. In 20, flame-shaped and round hemorrhages were seen. These favored the posterior pole, were rarely pre-retinal and almost never occurred in the vitreous. Repeated examinations are essential as the retinal picture varies with the anemia and hemorrhages may appear or disappear within 48 hours. The veins become engorged and tortuous, and arteries and veins are of a similar yellowish color. Exudative white spots are frequent. Papilloretinal edema was observed in eight cases. Isolated, scattered hemorrhages with a clear center are pathognomonic and were noted in half the cases. Retinopathy with hemorrhages occurred with the same frequency in acute myeloblastic and acute lymphoblastic anemia. The average survival period in patients with retinopathy was about ten months, while those without retinopathy survived three times as long. Histologic studies of 11 eyes showed leukemic infiltration of the choroid at the posterior pole and in the perivascular spaces.

James E. Lebensohn.

Radnot, M., and Wallner, E. **Newcastle virus disease of man.** *Klin. Monatsbl. f. Augenh.* 119:477-480, 1951.

Newcastle virus disease is not as rare in man as has been thought. The authors report 11 cases, which brings the reported total to 54. Probably many more are unrecognized. There is swelling of the lids and conjunctival injection with very little

secretion. This disappears after six to eight days, and cultures are negative. The preauricular glands are swollen and painful, headache and fever are present. Chickens and turkeys are the fowls most commonly affected and only through intimate contact with the diseased birds does man acquire the disease. There is no leucocytosis nor lymphocytosis, but a transitory monocytosis may exist. Penicillin and aureomycin are therapeutically ineffectual.

B. T. Haessler.

Rieger, H. **Toxoplasmosis acquired in adult life.** *Klin. Monatsbl. f. Augenh.* 119: 459-476, 1951.

Adult toxoplasmosis is generally a latent disease that rarely leads to death and is demonstrable only by positive skin and serum reactions. This latent form may become active under the special stresses of hunger, pregnancy or disease. Then it is manifest in the eye as a central external exudative retinitis. Four such cases are reported by Rieger. There was involvement of the retinal vessels and a condition resembling circinate retinitis in all the patients and one patient also had paresis of the inferior oblique. Skin tests and serum reaction (Sabin) were positive in all cases. Rieger considers central external exudative retinitis as a toxoplasmotic retinitis of the adult, and believes it should be so termed. Some cases of perivasculitis of the retina which have been thought to be due to tuberculosis are probably toxoplasmotic in origin, and certainly all cases of infectious disease of the liver should be tested for toxoplasmosis. (3 figures)

B. T. Haessler.

Tanoue, Akira. **Ocular symptoms of Basedow's disease.** *Acta Soc. Ophth. Japan* 56:1-9, 55-60, Jan., 1952.

In 13 cases of typical Basedow's disease, the course of dark adaptation was followed and a decreased light sense was

found in 9 of the 13 patients. In four of the nine patients there was a recovery of light sense after thyroidectomy and in three after the administration of vitamin A. In the other two patients recovery resulted only after a combination of vitamin and surgical treatment.

In 30 cases of Basedow's disease the author performed a Maddox rod test at 20 cm. and 5 m. He found no exophoria in any of the patients and therefore concluded that Moebius' sign has nothing to do with a functional insufficiency of the internal rectus muscle.

Yukihiko Mitsui.

Thies, Oscar. **The mucocutaneous ocular syndrome of Fuchs.** *Klin. Monatsbl. f. Augenh.* 119:486-494, 1951.

In 1950 Thies described two cases of exudative erythema multiforme (*Klin. Monatsbl. f. Augenh.* 116) affecting the eyes. In the present paper he attempts to correlate this disease with that described by the dermatologist Proppe in the *Arch. f. Derm.* 183:392, and called by him the acute mucocutaneous ocular syndrome of Fuchs. It is a distinct entity and not to be confused with pemphigus or the symptom complex known as ophthalmia lenta (Gilbert). The cyanosis and swelling of the face, ulceration of mucous membranes, the severe conjunctivitis, fever, headache and characteristic exanthem heal completely within four weeks and there are no recurrences. Proppe suggests that all the disease complexes described by various workers which fit this clinical picture, should be unified under the name mucocutaneous ocular syndrome of Fuchs.

B. T. Haessler.

Walsh, Frank B. **Papilledema associated with increased intracranial pressure in Addison's disease.** *A.M.A. Arch. Ophth.* 47:86, Jan., 1952.

Thrombosis of the intracranial dural

sinuses was the probable explanation for the ocular signs in this probably unique case of papilledema in Addison's disease.

R. W. Danielson.

19

CONGENITAL DEFORMITIES, HEREDITY

Bock, R. H. **Epibulbar dermoids associated with malformation of one half of the face.** *Ophthalmologica* 122:86-90, Aug., 1951.

In one of identical twins multiple epibulbar dermolipomas were associated with marked underdevelopment of one side of the face. The other twin was normal in every respect.

Peter C. Kronfeld.

Chinaglia, V., and Bello, D. **Cranio-orbito-facial dysostosis (a clinical and etiological study, with particular reference to Crouzon's disease).** *Ann. di ottal. e clin. ocul.* 77:383-417, Oct., 1951.

The authors report three cases of dysostosis of the cranium and face which they classify as Crouzon's craniofacial dysostosis (ocular hypertelorism). The patients were unrelated, and in only one case was there any possibility that the disease might have been hereditary or familial. From the clinical and radiologic data, the authors conclude that an inflammatory process in prenatal life had caused precocious synostosis of the cranial sutures with secondary intracranial hypertension, ocular lesions, and anomalies in the structure of the face. Further investigation is needed to determine whether this hypothesis can be related to what is now known about ocular embryopathies of viral origin. (References)

Harry K. Messenger.

Sussman, I. **A new variety of the syndrome of Bardet-Biedel: adiposogenital dystrophy, external ophthalmoplegia, polydactyly, mental deficiency, and hypo-**

plasia of the hypothalar eminences. *Arch. d'ophth.* 11:661-676, 1951.

Sussman reports the case of a girl, 19 years old, whose parents are first cousins and who presented an external ophthalmoplegia of the supranuclear type with bilateral ptosis, adiposogenital dystrophy, polydactyly, mental deficiency, and hypoplasia of the hypothalar eminences. He considers that the case should be considered a variant of the Bardet-Biedl syndrome in spite of the absence of retinitis pigmentosa and the fact that he could find no reference in the literature to an association of hypoplasia of the hypothalar eminences with the syndrome. He describes the typical syndrome and its variants in detail and mentions the relative frequency of the variants. A family tree of the patient is included and a black and white photograph showing the obesity, the small stature, the polydactyly, and the microcephaly. (Extensive references)

P. Thygeson.

20

HYGIENE, SOCIOLOGY, EDUCATION, AND HISTORY

Biró, I. **Ophthalmologic considerations of consanguineous marriage.** *Klin. Monatsbl. f. Augenh.* 119:585-596, 1951.

In consanguineous marriages, those characteristics, normal or pathologic, occur in the offspring which in the parents were present in heterozygous form and were therefore not manifestly apparent. The greater the number of pathologic recessive characteristics, the greater will be the hereditary defects in a certain percentage of the children. It is not the degree of consanguinity that determines complications in the offspring, but the fact that the parents carry such a pathologic heterozygous recessive that it will appear in the offspring as a homozygote recessive.

The ophthalmologic literature has many

examples of diseases that resulted from consanguinity. Most of them consist of cerebro-retinal or retinal diseases, but many other disturbances have also been listed. Biró gives 16 case histories of patients with the following diseases: pigment degeneration of the retina, degeneration of the macula, albinism (in 25 to 33 percent of cases of albinism consanguinity of the parents has been proven), dystrophia adoposo-genitalis with horizontal nystagmus, congenital dislocation of the lens, blepharochalasis in two sisters, monocular high myopia with anisometropia, and high hypertropia.

In 1946, Sos made an extensive study of consanguinity in a remote mountainous region of Hungary. In one family of 125 persons there were 29 consanguineous marriages; 40 of these could not be examined, of the other 86, 23 individuals were completely and 10 partially incapacitated from earning a living by cretenism, blindness, deafness and other defects. Biró concludes that the harm done by consanguineous marriage to individuals and communities far outweighs the possible advantages of conserving special gifts by heredity. (2 figures, references)

B. T. Haessler.

Duguet, J., and Mercier, A. **Ophthalmic problems created by stratospheric flying and supersonic speeds.** *Ann. d'ocul.* 184: 969-993, Nov., 1951.

A plane moving faster than sound could easily collide with another plane before the pilot could make corrective movement. In the two and one-half seconds which are necessary for a pilot to see an approaching object, orient his plane, look at the dashboard, and alter the controls, his plane traveling at the speed of 1,000 miles per hour would have traveled more than a half mile. This time is further modified by the location and amount of the retinal stimulus, accommodation, convergence and fatigue. When the tempera-

ture is 15°C. at sea level it is -56°C. at a height of 11,000 m. The external eye begins to freeze in 90 seconds at -40°C. Supersonic speeds begin at 760 miles per hour near sea level. Sonic and supersonic vibrations from within the plane and from the external air unable to escape the plane, may affect the eyes in two ways. The first is primarily a disturbance or fixation with the body as an elastic mass which absorbs these vibrations more or less successfully. The second type of vibration is called shock and may be associated with traumatic lesions ranging from slight hemorrhage to rupture of the eyeball. At high speeds angular deviation is of less importance than the abnormal smallness of distant objects. Helmet protection against burns of the face and eyes is necessary in parachute landings from stratospheric heights, because air friction against the body may produce temperatures as high as 600°C. Suitable protection is also necessary against glare which is ten times greater at stratospheric heights than at sea level. (7 figures, references)

Chas. A. Bahn.

Granal, Maurice. **Trachoma in Roussillon.** *Rev. intern. du trachome* 28:7-20, 1952.

Indigenous trachoma, once rampant in this French district, has practically disappeared. The drainage of marshlands which resulted in an improved standard of living, not prophylaxis or treatment, accounts for the present favorable status.

James E. Lebensohn.

King, J. H., Jr. **Research in the Army as it pertains to ophthalmology.** *Tr. Am. Acad. Ophth.* pp. 880-885, Nov.-Dec., 1951.

At present there are 218 research contracts with nonprofit organizations and 342 Army sponsored projects. Ocular research units are interested in visual standards in the different branches of military services, optical equipment, malingering,

ophthalmic training, protective goggles, and the treatment of ocular injuries.

Chas. A. Bahn.

Maxwell, Earl. **Research in the Air Force as it relates to ophthalmology.** Tr. Am. Acad. Ophth. pp. 872-880, Nov.-Dec., 1951.

With increasing speeds and altitudes in aviation the research problems involving vision have tremendously increased in importance, number, and complexity. These include such varied subjects as windshield and cockpit design, runway operations and the best location of bombardiers and gunners, as well as visual efficiency tests for pilots. Fighter plane pilots with 20/10 vision have a marked advantage over those with 20/20 vision. The use of corrective glasses has many disadvantages. Contact glasses are being used experimentally by the British in selected cases and their use is being studied by American pilots. Ocular protection from shock waves and a better ophthalmic understanding of the prone position for navigators are of great importance. The best means of protection against blackouts and scotomata caused by decreased barometric pressure and excessive glare, which is approximately ten times greater than at sea level, are problems still to be studied.

Chas. A. Bahn.

Schilling, C. W. **Visual research in the United States Navy.** Tr. Am. Acad. Ophth. pp. 868-872, Nov.-Dec., 1951.

Among the basic problems studied by the Navy are tests for night blindness, the determination of visual thresholds, the characteristics of retinal responses, the

development and evaluation of multitests and screening devices for military personnel. Many of the investigations require the coordinated efforts of physicians, psychologists, and physiologists. The estimation and correction of refractive errors and the constructive use of monocular and binocular instruments in naval services have been studied. The technical problems involved in the construction and use of instruments on panels, as in airplanes and submarines, are explained to illustrate the varied character of Navy visual research.

Chas. A. Bahn.

Tabone, V. **Anti-trachoma campaign in Gozo.** Rev. intern. du trachome 28:55-61, 1952.

The island of Gozo near Malta has a population of about 28,000. A survey in 1948 showed that school children had the greatest incidence of trachoma. Of 4,058, 721 were trachomatous. Sodium sulfacetamide was the treatment employed. Full oral doses were given for ten days, the 30-percent solution was instilled three times daily and the 6-percent ointment was used at night. After 22 months, only six cases of trachoma were seen in the schools.

James E. Lebensohn.

Wilczek, M. **Prevention of ophthalmia neonatorum with penicillin.** Klinika Oczna 21:79-81, 1951.

The author describes his results on 2,000 new born infants using penicillin emulsion in paraffin oil with beeswax, 5,000 units per mil. In no case was there an infection or even irritation of the eyes.

Sylvan Brandon.

NEWS ITEMS

Edited by DONALD J. LYLE, M.D.
601 Union Trust Building, Cincinnati 2

News items should reach the editor by the 12th of the month but, to receive adequate publicity, notices of postgraduate courses, meetings, and so forth should be received at least three months before the date of occurrence.

DEATHS

Dr. Samuel Faust Nabers, Birmingham, Alabama, died December 15, 1951, aged 77 years.

ANNOUNCEMENTS

ORTHOPTIC COURSE

The American Orthoptic Council announces that its annual intensive course in orthoptics will be presented in St. Louis, Missouri, from July 1, 1952, through August 30, 1952. The tuition is \$150.00, \$50.00 of which is payable at the time of application as a matriculation fee.

The council requires a minimum of nine months for certification and those taking the course receive credit for two months. The remainder of the training time is spent in practical work similar to an internship at any one of a number of approved training places. All practical training must be completed under the supervision of an orthoptic technician who has received the council's certificate.

The council endeavors to place all students for practical training if they have not already made such arrangements prior to taking the course. Because of administrative reasons, few training places will accept students for training for periods of less than nine months.

Inquiries for further information or for applications may be addressed to Dr. Richard G. Scobee, American Orthoptic Council, 640 South Kingshighway, St. Louis 10, Missouri.

ORTHOPTIC EXAMINATIONS

The annual examination of orthoptic technicians by the American Orthoptic Council will be conducted in September and October, 1952.

The written examination will be nonassembled and will be on Thursday, September 4th, in certain assigned cities, and will be proctored by designated ophthalmologists.

The oral and practical examinations will be on Saturday, October 11th, in Chicago, just preceding the meeting of the American Academy of Ophthalmology and Otolaryngology.

Application for examination will be received by the office of the secretary of the American Orthoptic Council, Dr. Frank D. Costenbader, 1605 22nd Street, N.W., Washington 8, D.C., and must be accompanied by the examination fee of \$30.00. Applications will not be accepted after July 1, 1952.

BASIC COURSE IN OPHTHALMOLOGY

The Department of Ophthalmology of Washington University's School of Medicine is in the process

of forming its 1952-1953 class for the basic course in ophthalmology. The next session begins September 15, 1952, and ends May 15, 1953. Tuition is \$800.00 and the course is approved by the Veterans Administration. Instruction includes 393 hours of didactic work and 759 hours of clinical work.

With the clinical background gained during the course, the average student can usually take full advantage of a residency and will require close supervision chiefly for surgical work. The course is limited to an enrollment of 12.

All inquiries or applications should be addressed to: Dr. Richard G. Scobee, director of graduate training in ophthalmology, 640 South Kingshighway, St. Louis 10, Missouri.

YALE POSTGRADUATE COURSE

Dr. Charles Schepens, in charge of the retinal service, Massachusetts Eye and Ear Infirmary, Boston, was the guest speaker at the Yale University School of Medicine Postgraduate Course in Ophthalmology on March 14th. His subject was "Retinal separations." Dr. Schepens reviewed a concept of the mechanism of retinal separation and showed a motion picture of his method for localization of tears, and colored still Kodachromes of retinal separations. Also, his surgical treatments were outlined.

Many questions and comments followed. Dr. Alexander Van Heuven, who introduced the speaker, felt that choroidal detachments following retinal separation were even more frequent than quoted by Dr. Schepens. Dr. Eugene Blake asked if Dr. Schepens had ever heard of or seen holes in toxemia of pregnancy. The speaker said he had not. Dr. Gregory Flynn asked the order of treatment of a patient with a cataract obscuring a known separation. Dr. Schepens said he would do the separation surgery first and attempt an intracapsular as the second step. Dr. Francis P. Guida asked about scleral ectasia complicating separations. Dr. Schepens favored partial thickness removal of the sclera preceded by diathermy before closure.

The meeting was preceded by a clinical case of a peripheral separation that was flat on the first dressing and the patient was therefore permitted to be up out of bed on the sixth postoperative day with a good result.

On February 29th, Dr. Frederick A. Wies was speaker at the postgraduate course. His subject was "So-called low tension glaucoma." He reviewed the literature on this type of glaucoma including past and present ideas on this disease and gave a detailed description of a clinical case taken from his own

office. A lively discussion followed with principal comments and discussion led by Dr. Eugene M. Blake.

The meeting was preceded by an unusual case of glaucoma in a 21-year-old white man who presented both serious diagnostic and therapeutic problems.

COURSE IN PSYCHIATRY AND NEUROLOGY

The University of California School of Medicine announces a postgraduate course in psychiatry and neurology to be given at the Langley Porter Clinic, San Francisco, August 25 through October 31, 1952. The course is open only to qualified physicians, and the fee of \$200.00 is payable in advance.

For further information, write to Dr. Stacy R. Mettler, head of postgraduate instruction, Medical Extension, University of California Medical Center, San Francisco 22, California.

MISCELLANEOUS

CONFERENCE ON TRACHOMA

When the committee on trachoma of the World Health Organization began its first session in Geneva on March 3rd, trachoma experts from the United States, Tunisia, Portugal, Morocco, Japan, Italy, and Egypt were in attendance. Subjects on the agenda for the meeting were: measures for control of trachoma, particularly among children; modern methods of treatment; international co-ordination of scientific research; and prevention of spread of trachoma through international traffic.

OCULAR MOTILITY COURSE

A postgraduate course in "Ocular motility" was given at the Percy Jones Army Hospital, Battle Creek, Michigan, under the direction of Col. Arnold A. Albright (MC) on March 12th to 14th. On the faculty were: Dr. Richard G. Scobee, St. Louis; Dr. James D. Sleight, Battle Creek; Dr. Don Marshall, Kalamazoo; and Miss Edith Roth, orthoptist, Percy Jones Army Hospital.

MASSACHUSETTS ALUMNI MEETING

The annual meeting of the Massachusetts Eye and Ear Alumni Association was held on April 15th and 16th at the Massachusetts Eye and Ear Infirmary, Boston. On Tuesday, the program included a surgical clinic in the morning and the presentation of the following papers at the afternoon and evening sessions:

"Some aspects of narrow-angle glaucoma," Dr. Paul A. Chandler; "Low-tension glaucoma," Dr. W. Morton Grant; "Flutterlike oscillations of the eyes and ocular dysmetria," Dr. David G. Cogan; "Plastic surgery of the eyelids," Dr. Garrett L. Sullivan; "Burns of the eye and adnexa," Dr. Brendan D. Leahey; "Biographical sketch of William MacKenzie," Dr. David Johnson; "Basic aspects of visual field study," Dr. Hugo L. Blair, Mayo Clinic, Rochester, Minnesota. Dr. William P. Beetham presided at this meeting.

Following the surgical clinic on Wednesday morning, Dr. Albert N. Lemoine presided at the afternoon session at which the following papers were presented:

"Electron microscopy in biology and medicine," M. A. Jakus; "Clinical application of flicker fusion fields," Dr. Albert N. Lemoine, Jr.; "Adherent rectus syndrome," Dr. Lorand V. Johnson; "Visual problems associated with exposure to atomic flash," Dr. Gustav C. Bahn; "An anomaly of retinal vessels," Dr. Mahlon T. Easton; "An unusual type of degenerative retinopathy," Dr. Hugh D. Donahue. Dr. Julian F. Chisholm, Jr., presented a moving picture on "An unusual eye injury."

SOCIETIES

PENNSYLVANIA ACADEMY

Guest speakers at the annual meeting of the Pennsylvania Academy of Ophthalmology and Otolaryngology on May 8th through 11th at the Galen Hall Hotel, Wernersville, were: Dr. M. Royden Astley, Philadelphia; Dr. Ben H. Senturia, St. Louis; Dr. O. E. Hallberg, Rochester, Minnesota; Dr. Herman Elwyn, New York; Dr. James B. Costen, St. Louis; Dr. Lawrence R. Boies, Minneapolis; Dr. Alton E. Braley, Iowa City; Dr. Edmund B. Spaeth, Philadelphia; Dr. Dean M. Lierle, Iowa City; Dr. William Councilman Owens, Baltimore; Dr. Paul A. Chandler, Boston.

BROOKLYN MEETING

At the 120th regular meeting of the Brooklyn Ophthalmological Society, the following case reports were presented:

"A case of iritis simulating a solitary tubercle of the iris," Dr. Arthur Shainhouse; "Toxic bilateral optic neuritis: Probably due to chloramphenicol," Dr. Nathaniel R. Katlan; "Congenital ocular facial palsy," Dr. Aaron Roth; "Lymphosarcoma of the right orbit, reticulin-cell type," Dr. Benedict Rizzuti; "Corneal dystrophy: Possible Bowen's disease," Dr. Martin Ackerman; "Lymphosarcoma of orbits," Dr. George A. Graham; "Encysted glass foreign body of eyelid and radiologic study of glass foreign bodies," Dr. Regina Gilroy.

READING GUEST SPEAKER

Dr. P. Robb McDonald, Philadelphia, was guest speaker at the 123rd regular meeting of the Reading (Pennsylvania) Eye, Ear, Nose, and Throat Society. Dr. McDonald spoke on "The use and abuse of miotics and mydriatics."

OFFICERS OF MEXICAN SOCIETY

Officers elected by the Mexican Society of Ophthalmology to serve for the following year are: President, Dr. Daniel Silva; vice-president, Dr. Manuel de Rivas Cherié; permanent secretary, Dr. Raúl A. Chavira; annual secretary, Dr. Robert Quiróz B.; treasurer, Dr. Jorge Meyrán; director of the society's publication, Dr. M. Puig Solanes; commission of honor, Dr. Lino Vergara, Dr. Abelardo Zertuche, and Dr. Ramón Olivera López; commission of admission, Dr. Armando Ramírez, Dr. Teófilo Manuel Agundis, and Dr. Francisco Arenas.

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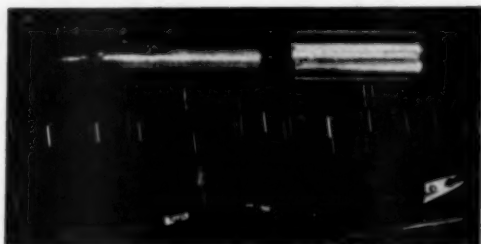
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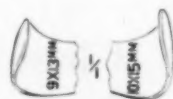
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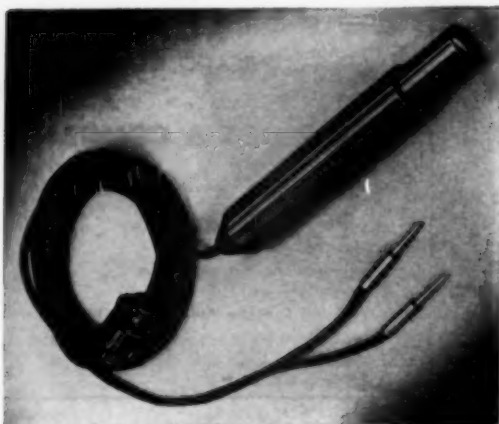
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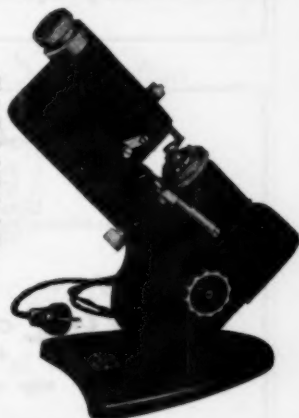
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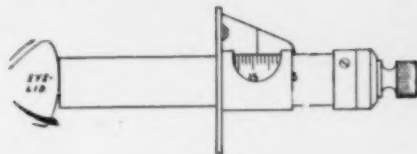
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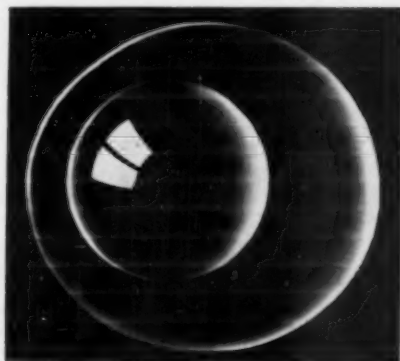
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THE LUDWIG VON SALLMANN

Proctor Medal Award

PROCEEDINGS

of the

Association for Research in Ophthalmology, Inc.

Twentieth Meeting

Atlantic City, New Jersey

June 13 and 14, 1951

* * * *

For a complete table of contents see page one

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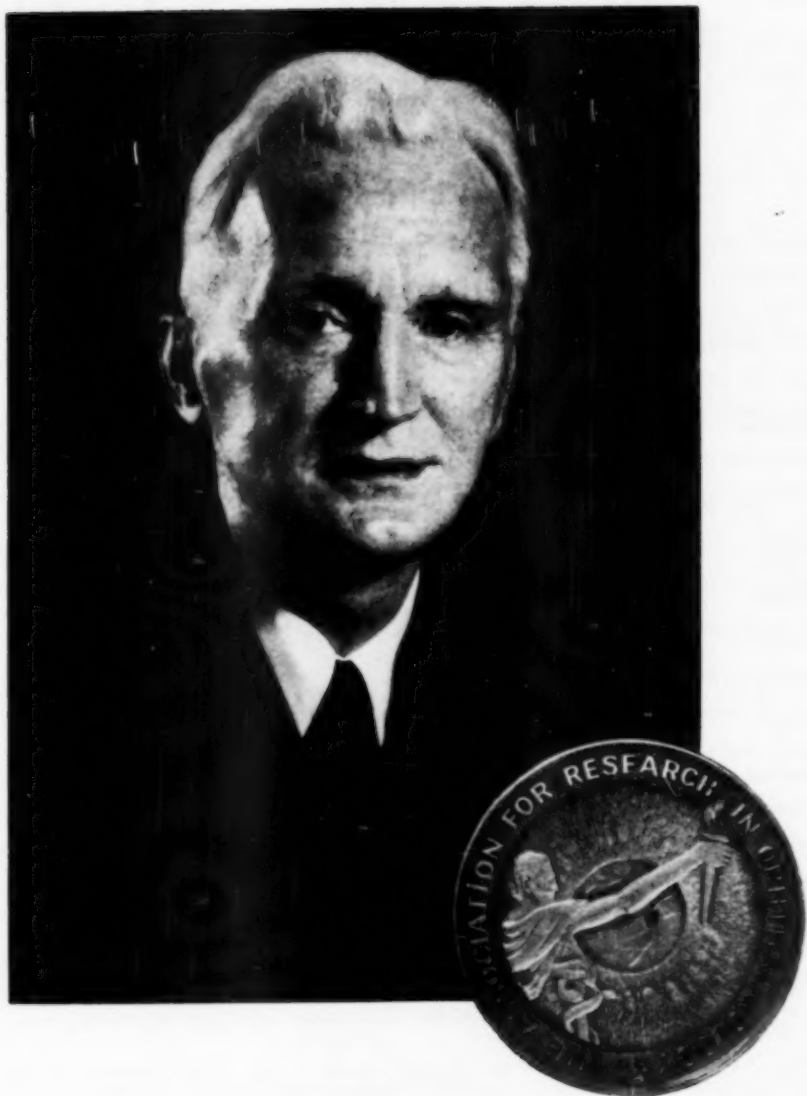
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PROCEEDINGS OF THE ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY

Twentieth Meeting, Atlantic City, New Jersey, June 13 and 14, 1951

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LUDWIG VON SALLMANN, M.D.

REMARKS MADE ON THE ACCEPTANCE OF
THE PROCTOR MEDAL AWARD

June 14, 1951

LUDWIG VON SALLMANN, M.D.

New York

When I read two years ago that Jonas Friedenwald had been elected the first recipient of the Proctor Medal, I felt, as we all did, that no better selection could have been made by the committee and the trustees of the association, in view of the scientific weight of his numerous contributions to basic fields in ophthalmology. We all realized then that this election defined the award as one ranking high among symbols of recognition in medicine.

Last year, when, in San Francisco, Phillips Thygeson was awarded the medal for successful research work, there was again among us the undivided feeling of profound satisfaction, since Dr. Thygeson had enriched our knowledge in several important respects by extensive laboratory studies, field studies, and clinical work and, like Dr. Friedenwald, had stimulated many of his associates by his spirit of sacrifice and endurance and by his endless search for ways to deepen clinical concepts in hard investigative labor.

For obvious reasons it would be an extremely embarrassing situation for me if I were to stand here now alone to receive the Proctor Medal for personal merit. It is my very good fortune that I don't feel alone at all but surrounded by an exquisite imagery of friends, or rather by an imagery of the actions of these friends who have been most influential in forming in me the kind of curiosity which makes life in the biologic research laboratory so delightful and fascinating.

There was the guidance and mentorship of Arnold Knapp which I shall cherish for the rest of my days, the encouragement and understanding of John Dunnington and Al Reese, the inspiration and enlightenment

from the accomplishments of outstanding research workers in this country, the boundless stimulation which I have experienced by the informal exchange of thoughts in neighborly conversation with such excellent men as Zacharias Dische, George Smelser, Karl Meyer, Seymour Halbert, all of them possessed by this magnificent disregard for personal advantage and by selfless devotion to a great work.

Last, but not least, there was and is the most pleasant association with younger investigators and co-workers, none of whom I should wish to have missed in the course of these colorful years. It fills me with joyful elation and with pride to be a part and product of such an imagery and to be thus awarded under the protection of this splendid constellation of powerful influences.

As the years go by, one becomes increasingly aware of the determinants which form an individual's interest and ambition. In the last 12 years the importance of investigative work in research laboratories has been demonstrated clearly to me by the endeavors and achievements of those men in this country of whom I made mention, and of others.

Before that, in a long stretch of 20 years, the spirit of Ernst Fuchs, alive in his pupils and associates, Dimmer, Meller, and Lindner, and the personalities of these teachers, acted upon me and others of my generation to create in us primarily a healthy interest in clinical investigative work on a histopathologic background. Under their auspices, clinical studies and early experimental work on the herpes problems were undertaken.

Lindner's contribution to cylinder retinoscopy provided the tools for specialized investigations on astigmatism, and his concept of the part played by the vitreous in the

pathogenesis of retinal and choroidal detachment aroused my interest in studying the physiology and physicochemistry of this rather neglected portion of the eye.

Personal contact and collaboration with men from other departments could be utilized to mutual advantage in the clinical use of radium for the treatment of eye disease; connections between blood pressure and intraocular pressure and the significance of ocular changes in hypertensive disease could be explored clinically and histologically.

The appointment as acting head of the Eye Department of the Peking Union Medical College, 1930 to 1931, taught me to use what I had learned in the grand eye department in Vienna, and to use it independently, far away from home soil.

The working conditions at the Eye Hospital in Vienna and the tradition of the school limited the facilities for complicated laboratory work, especially after the war had ended in 1918 with the disastrous dissection of the monarchy.

It was for me a unique and inestimably rewarding experience, therefore, to work for a year in the laboratory of the Knapp Memorial Hospital in New York, and then to join the research group of the Department of Ophthalmology in the College of Physicians and Surgeons with its unequalled opportunities for team work under the leadership of Phillips Thygeson.

I assume that many of you are familiar with the precarious situation in which one finds oneself in a new working place, overlaid as it inevitably is with the initial oppressiveness of the unknown and the strange. It was Dr. Thygeson's helpfulness and his gift for organization which quickly eliminated psychological obstacles and made me soon feel at home in the laboratories and with the men at work in them.

Karl Meyer had then completed his well-known studies on certain biochemical aspects of the vitreous and it was somewhat in line with this research effort that I returned to investigations on the colloid chemistry of

the vitreous, a subject which has remained attractive to me throughout the years. In vitro studies on turgescence, shrinkage, turgescence pressure, and other hydrogel qualities of this complex colloid system were extended to studies on its permeability, to animal experimental work on the hydrogen ion concentration in the fluids of the eye, and in cooperation with Dan Moore, to studies on the electrophoretic pattern of the proteins in such fluids; later this work included experiments on resorption from the vitreous space.

The possibility of obtaining expert advice on ophthalmologic problems from members of other laboratory groups nearby was put to good use on several occasions, in pharmacologic studies, for example, and in the work on radio-autographic techniques as applied to the eye.

In war time the accent in medical research tends to shift. It was due in part to the war situation that the workers in the Knapp Memorial Laboratory indulged for several years in experimental and clinical studies on the applicability of antibiotics to the eye. Fortunately, the practical results of these investigations, which had been suggested by Dr. Thygeson, were not limited to war conditions and the work continues in the hands of other investigators of this laboratory group.

Similar conditions of general nature, like those which led to the experimental work with antibiotics, influenced the undertaking of studies on radiation damage to the eye. Former clinical experience with radium and x-radiations added to the appeal of a recent offer of Professor Failla to concentrate a part of the activities of the laboratory, with the support of the Atomic Energy Commission, on investigative work on radiation cataract. This proposition was welcomed with particular eagerness since it included the opportunity to join arms with a biochemist of far-reaching specific knowledge in the person of Dr. Dische.

Whatever I have said concerning the various lines of my activity may be completely

irrelevant. I have not tried to outline my own pursuits as facts per se, nor to provide data for an autobiographic sketch which in my case could be in no way of general interest. On the contrary, I have sought to demonstrate by an example how negligibly individual efforts rate as compared to conditioning factors in general, and specifically to the principles of a system which provides opportunity for participation in research work in its wider sense proceeding from the interdependence of a host of apparently unconnected facets of knowledge.

I do not know of the existence anywhere in the world of any other scientific society in ophthalmology which was founded for the purpose of integrating basic work with

clinical problems. In studying the published documents of the explorative scholarship of this society, one cannot escape the impression that this basic idea has proven to be of immense value again and again.

The gap between the island of our rather small specialty and the wide shores of general biology, biochemistry, and other basic sciences, has been bridged successfully in many instances by members of this society and, if one is allowed to contribute to these efforts even to an infinitesimal extent, he should be filled with gratitude for the opportunity which enabled him to do so. Certainly this gratitude is pervading me together with the other one for the great honor you have bestowed on our group.

BIOGRAPHICAL DATA

LUDWIG J. K. VON SALLMANN, M.D.

DATE AND PLACE OF BIRTH

June 8, 1892, in Vienna

EDUCATION

M.D., Medical School, University of Vienna, 1919

Medical Department, University of Vienna, 1919-1920

Resident in 2nd Eye Department, University of Vienna Medical School, 1920-1923

POSITIONS

Attending ophthalmologist and assistant, Medical School, Vienna, 1923-1930

Associate professor ophthalmology and head of Department of Ophthalmology, Medical School, Peking Union, 1930-1931

Docent, Department of Ophthalmology, Medical School, Vienna, 1931-1938

Head, Eye Department, Empress Elizabeth Hospital, Vienna, 1938

Director, Laboratory Herman Knapp Eye Hospital, New York, 1939

Research associate, College of Physicians and Surgeons, Columbia University, New York, 1940-1941

Assistant professor of ophthalmology, 1941-1945

Associate professor of ophthalmology, 1946

Assistant attending ophthalmologist, Institute of Ophthalmology, Presbyterian Hospital, New York, 1941-1945

SOCIETIES

Association for Research in Ophthalmology

American Medical Association

American Academy of Ophthalmology and Otolaryngology

New York Medical Society

Pan-American Association of Ophthalmology

Greek Ophthalmological Society

TOTAL PUBLICATIONS—147

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AQUEOUS VEINS AND CONTACT LENSES*

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The question as to why different eyes show varying degrees of tolerance to the refraction-correcting contact lens has been approached from different viewpoints: Mechanical-optical, cell-physiologic effects on the corneal tissues, chemical alterations on the corneal tissues and in the aqueous humor were assumed. Since the elimination of aqueous humor can now be studied biomicroscopically,¹ a new approach to this problem presents itself.

The aqueous veins and Schlemm's canal together form a physiologic unit² and, therefore, changes occurring in Schlemm's canal under the effect of the gonioscopic contact lens should also be considered.

The effect of gonioscopic contact lenses on the blood content of the canal of Schlemm has been studied by Trantas,³ Troncoso,⁴ Sugar,^{5, 6} Bangerter and Goldmann,⁷ Kron-

feld and associates,⁸ Busacca,⁹ Moreu,¹⁰ and many others.

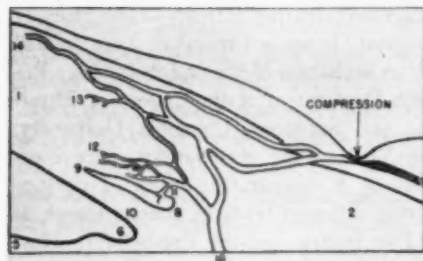
While Sugar found that the gonioscopic contact lens provoked influx of blood into the canal, Kronfeld observed that it may expel blood from the canal of Schlemm. An explanation of this discrepancy could be that Sugar might have happened to see more eyes with aqueous veins showing the blood-influx phenomenon, and Kronfeld more eyes showing the aqueous-influx phenomenon.

Characteristic phenomena are observed when the recipient vessel of an aqueous vein is compressed near its junction by means of a small cotton applicator or by a minute probe. Then, either one of the following effects may be observed (fig. 1):

1. Stratification, if present before compression, disappears quickly and the vessel becomes uniform in color and, soon, quite colorless. If so, this part of the vessel resembles a glass rod surrounded by semi-transparent porcelainlike scleral tissue; this aspect was originally^{1, 2} called the glass-rod phenomenon, a purely descriptive term which since has been replaced by a more unequivocal one: aqueous-influx phenomenon.¹¹

2. Compression of the recipient vessel near

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SCHEMATIC CROSS-SECTION



BIOMICROSCOPIC ASPECT

Fig. 1 (Ascher). *Aqueous-influx phenomenon*. After compression of the recipient vessel, clear fluid enters the blocked section and, in a reversal of current direction, expels the blood corpuscles out of the recipient vessel. Expulsion of red cells is the essence of the aqueous-influx phenomenon.

the entrance of an aqueous vein does not always produce expulsion of the blood; often the opposite phenomenon is found: while the current is slowed down, stopped, and even reversed, a colorless aqueous vein may become filled with blood (fig. 2). This expulsion of clear fluid and entrance of blood was formerly termed negative glass-rod phenomenon. Lately, the simpler and more precise term blood-influx phenomenon has been introduced.¹¹

When compression is released, in both instances, the former appearance will be restored; blood will reënter the space which, during compression, was waterclear, or the aqueous vein will become clear again if it was filled with blood during the compression.

An interesting phenomenon which may help the understanding of the effects of both gonioscopic and refraction-correcting con-

tact lenses on the blood content of the canal could be called the gonioscopic-lens-rocking effect of Busacca⁹ (fig. 3).

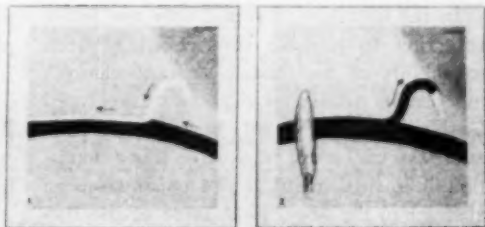
According to his description, it is characterized by entrance of blood into a sector of the canal opposite to the site of pressure application and, thus, confirms what has been assumed concerning the mechanism of the blood backflow phenomena toward, and into, the canal.¹²

A tentative explanation can be given now in assuming that, at the site of the pressure, communication between the canal and superficial blood vessels is temporarily interrupted and aqueous held inside the canal; while on the opposite side, where connections are not interfered with, blood can enter the canal.

Another explanation could be that the gonioscopic lens, pressing upon the eyeball,

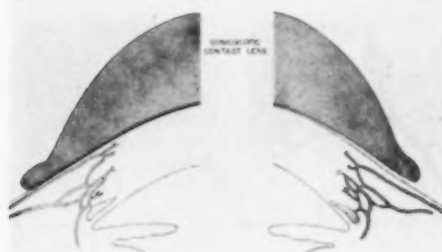


SCHEMATIC CROSS-SECTION



BIOMICROSCOPIC ASPECT

Fig. 2 (Ascher). *Blood-influx phenomenon*. After compression of the recipient vessel, red blood cells enter the aqueous vein in a direction opposite to that of the previous aqueous flow.



The canal contains aqueous humor on that side where the lens presses upon the eye-ball.

The canal contains blood on the opposite side where the lens leaves the episcleral veins undisturbed.

Fig. 3 (Ascher). The gonioscopic-lens-rocking-effect of Archimede Busacca (1945) results in a large-scale compression phenomenon and produces an increment of pressure on one side, and blood influx on the other side of the canal.

produces increased outflow of aqueous humor from the chamber into the canal which, on the side opposite to the pressure, will show less resistance to entrance of blood.

Interesting questions arise from Busacca's observation: whether eyes with the blood-influx phenomenon will react to the rocking test in the same way as those with an aqueous-influx phenomenon; whether glaucomatous eyes will react differently from those with normal intraocular pressure. It might be expected that, in glaucomatous eyes, the rocking test will not result in blood entrance unless eye pressure has previously been reduced by either miotics or surgery. Further study of the rocking test seems promising.

In the literature, I found only one paper referring to possible connections between tolerability of the contact lens and changes in aqueous veins: an expectation ventured by Neill¹³ who did not, however, describe any observations in support of this assumption. I learned about Neill's paper from an abstract in the May, 1949, issue of the *Excerpta Medica*.*

OWN OBSERVATIONS

Since January, 1949, aqueous veins of

contact-lens-wearing patients of the Murphy Memorial Group in Cincinnati were studied and, on invitation of the Ophthalmology Research Department of the College of Physicians and Surgeons, Columbia University, New York, these observations were completed by a comparative study of persons wearing different types of contact lenses, at the Eye Institute of the Presbyterian Hospital in New York, in December, 1949.

This study was supported in part by a grant from the Office of the Surgeon General to Columbia University, administered by Dr. George K. Smelser.

In the Columbia University Ophthalmology Department, we endeavored to observe, with the aid of a $\times 10$ magnifying loupe and on the corneal microscope, the effect of contact lenses on aqueous veins of dogs, rabbits, and guinea pigs, previously fitted with different types of contact lenses which were tolerated well in most cases.

Only one dog and two rabbits showed what could be considered the equivalent of aqueous veins as seen in human eyes; in all three eyes, however, these vessels became filled with red blood cells on insertion of the contact lens and immediately it became impossible to distinguish the direction of current.

On human eyes wearing standard lenses, that is, those with an uninterrupted scleral rim, the following changes were observed at varying intervals after insertion of the refraction-correcting contact lens:

1. In many, not in all, eyes studied, a reversal of current in the aqueous vein took place.

2. Cyanosis of aqueous veins and other conjunctival and episcleral veins and occasionally sludging in the aqueous veins occurred and the limbal and deeper capillaries became congested.

* In abstract No. 909 of the May, 1949, issue of the *Excerpta Medica*, Neill's middle and surnames were transposed so that he appears as Collins, N. J., instead of Neill, C. J.

3. Normal appearance was restored at varying intervals after removal of the refraction-correcting contact lens.

Reversal of current in aqueous veins when covered by a contact lens usually starts as soon as the latter is inserted; only in larger aqueous veins with a vigorous current, it may take some seconds or even minutes before the whole vessel shows a change in direction of flow of its contents; often, an ambiguous current may be observed at some distance from the limbus, the part near the limbus showing reversed direction of flow and the more peripheral part of the vessel continuing in the original direction.

Some minutes after insertion of the contact lens, many aqueous veins will show the direction of flow toward instead of from the limbus. To and fro movement and sludging may appear in parts of the vessel.

By this time, the aqueous veins show a markedly darker color in comparison to the ciliary and conjunctival arteries. The distinction, by color, between arterial and venous blood vessels on the surface of the eye, almost impossible in normal eyes,¹⁴ is easy under the influence of the contact lens. Not only aqueous veins but also regular conjunctival and subconjunctival veins become darker as time goes on. Finally, the reversed current in the aqueous veins will slow down and eventually stop.

At this stage which occurs after 10 to 60 minutes, occasionally even later, a sedimentation of the red blood cells may appear. This is the moment when the wearer of the contact lens usually complains of marked discomfort.

The sedimentation may be preceded by a more or less pronounced sludging of the blood current in the aqueous vein, similar to the pictures of sludging blood to be seen in Knisely's¹⁵ moving pictures of the mesenteric vessels of diseased animals. The difference between the phenomena referred to as sedimentation and sludging is, in the aqueous veins, that sedimentation occurs only where the current is completely or al-

most completely stagnant while sludging corresponds to conglomeration of red blood corpuscles which are yet moving although slowly.*

At the same time, the limbal, as well as the deeper capillary meshwork, becomes more and more congested; vessels not visible prior to insertion of the contact lens appear at different levels, the superficial ones more clearly outlined, the deeper ones more hazily visible. A slight purple hue surrounds the limbus at this time (figs. 4, 5, 6, and 7).

As soon as the contact lens is removed, the current in the aqueous veins resumes its previous direction, that is from the limbus toward the periphery, and sludging, sedimentation, cyanosis, and perilimbal congestion disappear within a few seconds or minutes. The clear content of the aqueous veins seems to force its way very vigorously and often all red blood cells disappear from the vessel for a period of 15, 30, or more minutes (fig. 8).

Similar phenomena occur after withdrawal of the gonioscopic contact lens: where a stratified aqueous vein had been located previous to the insertion of the gonioscope, Hobbs¹⁶ saw, after withdrawal of the gonioscope, a rapid return to normality indicated by reappearance of the stratification in the aqueous vein.

In the Columbia University Eye Institute, nine volunteers were available for 24 observations. The time from insertion of the lenses varied between 14 hours and 10 minutes, with one experiment extending over 14 hours, two over seven hours, five between seven and three hours, six lasting two hours, two between two and one hour, and eight, one hour or less.

Three volunteers were able to wear three different types of lenses, the standard lens, with the full scleral rim, the so-called lacrimal

*According to Robertson, Wolf, and Wolff,¹⁷ widespread sludging is compatible with good health. The cyanosis in the region covered by the contact lens, however, means more than a slowing-down of the blood current.

lens with an indentation at the 6- and 12-o'clock positions, and the "corneal" (Tuohy lens)¹⁷ which does not cover the limbus and adjacent conjunctiva. Four persons were fitted with both standard and lacrimal lenses and two more wore only standard lenses at the time of these observations.

The standard lens provoked a reversal of current in the aqueous veins in five out of 14 experiments performed. In five out of eight experiments with the lacrimal lens, the direction of current in the aqueous veins remained normal. Under the standard lens, normal current was retained in one experi-



Fig. 4 (Ascher). White woman, aged 27 years, left eye. Very large aqueous vein. (Photograph of colored drawing by Miss Jean Schuff, B.Sc., Department of Medical Art, College of Medicine, University of Cincinnati.)



Fig. 5 (Ascher). Thirty minutes after insertion of the contact lens, the red blood-cell content was increased and the current in the aqueous vein was reversed and slight sludging appeared. (From drawing by Miss Jean Schuff.)



Fig. 6 (Ascher). Forty-five minutes after insertion of the contact lens, the aqueous vein was full of red blood cells, of very dark color, the current was also reversed in one of its tributaries near the limbus, and the deep meshwork was congested. (From drawing by Miss Jean Schuff.)

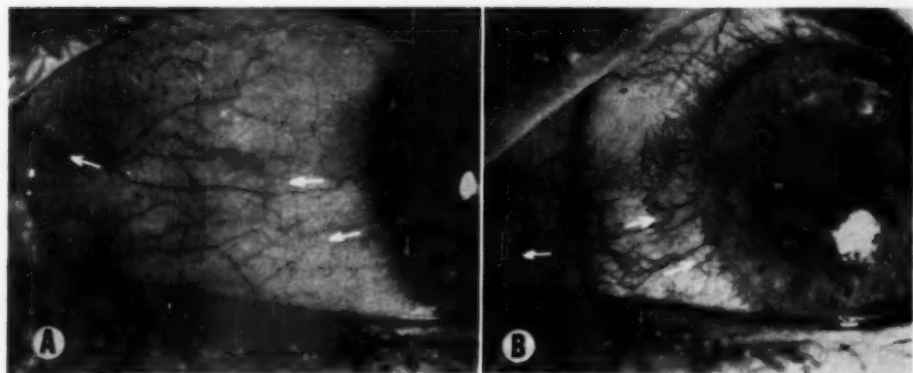


Fig. 7 (Ascher). Aqueous veins under the influence of the refraction-correcting contact lens. (A) Volunteer H. D. K., aged 23 years, left eye, two hours without contact lens. There are very few red blood cells, a rapid current, and normal direction in both aqueous veins (see arrows). (B) Same eye two hours after insertion of contact lens. There is an increase in red blood cells in both aqueous veins. The slow current is reversed with slight sludging. The limbal meshwork is congested. (Photographed at the Institute of Ophthalmology, Columbia University, December, 1949. Reproduced through the courtesy of Dr. G. K. Smelser and Mr. J. Lafayette.)



Fig. 8 (Ascher). Sixty minutes after insertion of the contact lens, the lens was removed. Immediately the red-cell content dropped and the original direction of flow returned. (From drawing by Miss Jean Schuff.)

ment for 14 hours, in one for four and one-half hours, in one for four hours, in two for three hours, in one for two hours, and in one for one hour. Under the lacrimal lens, normal current was preserved in one experiment for seven and one-half hours, in three for two hours or more, and in one experiment for at least 30 minutes.

The compression test on the recipient vessel was not performed on all of these eyes; there was, however, a coincidence between aqueous-influx phenomenon and normal direction of current under the contact lens in six experiments while reversed current under the contact lens corresponded to the blood-influx phenomenon in five experiments.

The location of the aqueous vein did not seem to be decisive; the aqueous vein showing normal current after 14 hours was a very deep one, another aqueous vein which preserved normal current for over seven hours was a superficial one.

An observation should be mentioned which for the time being cannot be explained: some aqueous veins showed reversed current in the part covered by the scleral rim of the contact lens while the uncovered part of the aqueous veins continued to show current in normal direction. The "watershed" was located at the edge of the contact lens and the vessel seemed to be empty for about 0.5 mm. both sides from this rim.

One volunteer, wearing lacrimal lenses in both eyes, showed, in her right eye, reversed current in the aqueous vein covered by the contact lens; in the left eye, an aqueous vein was located near the 12-o'clock position corresponding to the notch of the contact lens and this aqueous vein remained unaltered; this person noticed haze and halos earlier in her right eye (four to five hours) while the left eye could tolerate the contact lens up to seven hours without the appearance of halos.

Limless contact lenses (the "corneal lens" by M. W. Nugent and K. W. Tuohy) did not provoke reversed flow in the aqueous veins nor cyanosis of aqueous veins nor congestion of the deep meshwork.

The relative merits of different types of contact lenses shall not be considered here; we were only concerned with observing their effect on aqueous veins.

Filling of the contact lens with hyperosmotic solutions produced changes in the aqueous veins similar to those evoked by contact lens solutions of normal strength and by distilled water. The only difference was that with hyperosmotic solutions hyperemia of the deep meshwork, reversal of the normal current, and cyanosis of the aqueous veins occurred earlier than with normal-strength contact lens solutions.

One volunteer at the Presbyterian Hospital Eye Institute in New York, Dr. G. K. S., tolerated both standard and lacrimal lenses for many hours and preserved normal current in his aqueous vein; if, however, his lens was filled with tap water instead of 1.5-percent sodium bicarbonate solution, haze and halos developed rapidly and reversed current was observed in his aqueous vein, which, with proper contact lens solution, retained its normal current for long periods.

DISCUSSION

Discussing the essence of the sludging in aqueous veins under the influence of the refraction-correcting contact lens would be mere speculation at present; however, one may venture the expectation that changes in oxygen content, hydrogen-ion concentration, and plasma-protein fractions may be involved.

Two facts, however, should be stressed at present: one is that sludging in the aqueous veins, congestion in the limbal meshwork, and change of the bright red color of the blood to a dark red occur at a time when the wearer of the contact lens feels unable to tolerate the lens any longer; second, an observation by Cross¹⁸ that veiling under a

contact lens appeared less marked when a bubble was present under the lens, and that people who can tolerate a small air bubble without discomfort may be relieved of the greater trouble of blurred vision.

These two facts would indicate that lack of oxygen plays at least some part in the tolerability of the refraction-correcting contact lens.

Among the many suggestions made to alleviate veiling under the contact lens, Ridley's¹⁰ seemed to be promising: assuming that Sattler's veil was due to edema of the cornea and conjunctiva, he suggested using a hypertonic contact lens solution in order to produce dehydration of the edematous tissues.

The molar concentration of the lens fluid seems to be of lesser importance than mechanical factors; differences in osmotic concentration will soon be equalized by osmotic exchange of ions and water, respectively, through the membranes involved; changing local pressure conditions, however, will prevail as long as the contact lens remains inserted and will produce changes in the direction of current in the affected vessels similar to those described by Busacca.⁹ Corneal contact lenses will not elicit these alterations in flow but may interfere with gas exchange as any other contact lens will, although possibly to a lesser degree.

From the described observations, drawing of conclusions concerning the tolerability of the contact lenses would be premature; it seems, however, that persons who preserved normal current in their aqueous veins under the influence of the contact lens were able to tolerate them longer than those who showed reversed current.

The number of eyes observed does not suffice for drawing of conclusions concerning the correlation between compression test on the recipient vessel and changes in aqueous veins due to insertion of the refraction-correcting contact lens; it seems, however, that eyes with the aqueous-influx phenomenon do not easily show reversed

current in their aqueous veins while wearing the contact lens, and that reversed current is the rule in these aqueous veins which, prior to insertion of the contact lens, showed the blood-influx phenomenon.

Therefore, in addition to other effects of the contact lens, known or assumed, we have to realize that refraction-correcting contact lenses, even with very mild pressure on the conjunctival surface, may produce either the blood-influx or the aqueous-influx phenomenon and thus may decidedly interfere with normal elimination of aqueous humor.

In the first case, blood will be forced back into the aqueous veins and possibly as far as into the canal of Schlemm and will produce an unphysiologic situation in either of these structures; in the second case, outflow of aqueous humor will be blocked or at least retarded. In both cases, sufficient collateral pathways may be available in order to compensate for the alteration of the physiologic pressure gradients; in some instances, however, this may be impossible for anatomic reasons and, in these cases, the contact lens will not be well tolerated.

SUMMARY*

The question of why different eyes show varying degrees of tolerability to the refraction-correcting contact lens has been approached from different viewpoints. Since the aqueous-humor elimination can now be studied biomicroscopically, a new approach

to this problem presents itself.

The aqueous veins of contact-lens-wearing patients of the Murphy Memorial Group in Cincinnati and volunteers of the Ophthalmology Research Department of the College of Physicians and Surgeons, Columbia University, New York, showed, in many instances, a reversal of the direction of the aqueous humor, increase of red-cell content, cyanosis and sometimes stagnation in the part covered by the rim of the contact lens. Before complete stagnation occurred, sludging was observed in some of the aqueous veins.

The peak of these changes coincided with the time when the wearer of the contact lens complained of marked discomfort and was unable to wear his lens any longer.

The reversal of current of the aqueous veins under the contact lens cannot explain all phenomena interfering with the tolerability of the contact lens but if it occurs, it must produce an unphysiologic situation by blocking or at least retarding the normal elimination of intraocular fluid.

5 West Fourth Street.

* Footnote added during proof reading: Convincing proof of my conclusions was provided by recently published observations by A. Huggert (Increase of intraocular pressure when using contact lenses. *Acta Ophth.*, 29:474-482 (No. 4) 1951) who observed intraocular-pressure increase in 25 of 33 eyes wearing contact lenses with narrow haptic for 30 minutes; in nine of these eyes, the pressure increase amounted to 10 or more mm. Hg.

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DISCUSSION

DR. GEORGINA D. THEOBALD [Chicago]: I take this opportunity to show you a few microscopic slides of the canal of Schlemm and its connecting canals. These will help you to understand and to visualize the flow of aqueous from the anterior chamber, through the intratrabecular spaces, through the inner canals of Sonderman into the canal of Schlemm.

The aqueous leaves the canal of Schlemm by means of external collector channels which form a deep intrascleral plexus. The branches from this deep-intrascleral plexus may follow three paths:

(1) In the three eyes I examined, there were five to seven branches which emptied into the ciliary body—that is, vena vorticosae; (2) most of the branches run diagonally through the sclera, to empty into the anterior ciliary veins; (3) some run almost vertically to the surface of the sclera on their way to join the anterior ciliary veins; it is these latter branches of the deep intrascleral plexus which are seen as aqueous veins.

In the depths of the sclera are some arteries and veins which have no connection with the canal of Schlemm. The veins of this plexus which is designated as the intrascleral plexus (in contradistinction to deep intrascleral plexus) connect with the veins of the latter and furnish the blood seen in aqueous veins.

I have made many models of these connections, some of which I have shown you today. Normally there is no barrier to the outflow of aqueous from the anterior chamber to the anterior ciliary veins.

DR. LUDWIG VON SALLMANN (New York): Dr. Ascher offered a rather guarded opinion on the connection between disturbances in the circulation of the aqueous veins and of the vascular system in the anterior segment of the eye on one side and the tolerance of contact lenses on the other. I

think that recent experiments of Dr. Smelser and Miss Ozanics throw some light on these questions. Since Dr. Smelser cannot be here, I take the liberty of reporting very briefly the results of their latest experimental series which will be published in the near future.

Dr. Smelser found in a group of volunteers, by using contact lenses with tubular openings, that changes of the pH of the sublens fluid was an important factor in producing halos and that by preventing the shift of the pH in this fluid to the acid side, the visual disturbances and other signs of poor tolerance for the contact lens did not occur.

It would seem, then, that the changes which Dr. Ascher observed in the circulation of the episcleral vessels in connection with the wear of contact lenses is a coordinated sign and not of causative nature in respect to the development of blurred vision by the use of contact lenses. I wonder what Dr. Ascher thinks about this interpretation.

DR. JOSEPH I. PASCAL (New York): I want to ask Dr. Ascher whether any observations were made in cases of patients who wear lenses 10 or 12 hours comfortably with reference to any changes apparent at the end of that period; in other words, whether any work was done to determine whether the comfort which these people find by wearing contact lenses eight to 10 hours is in spite of this back-flow and other disturbances, or whether, in those cases, the eye adjusted itself to the lenses so that the disturbances disappear.

DR. JOHN M. McLEAN (New York): I would like to ask Dr. Ascher a couple of questions. It seems that he has demonstrated fairly clearly by the absence of this phenomenon when the scleral segment of the contact lens is not present, as in the lacrimal lens, or when there is no scleral segment

at all as in the so-called corneal lens, that this is a pressure phenomenon rather than a secondary result of some respiratory change.

I wonder, therefore, if he has been able to correlate a few possible clinical factors—for example, whether he has been able to correlate the degree of tolerance of contact lenses in different eyes with the number, if any, of aqueous veins in those eyes; whether it might be possible to predict that in certain patients with more and larger aqueous veins, contact lenses would be less tolerable than in patients with small ones, or if contact lenses would be tolerated better.

I would also like to inquire whether he has made a correlation between intraocular pressure before and after these changes have been caused by wearing of contact lenses. It seems that there is some potential connection which might or might not turn out to be significant in the change in surface aqueous circulation produced by these lenses.

DR. K. W. ASCHER (closing): I want to thank all the discussers very heartily. The beautiful slides of Dr. Theobald show the connections between the canal and the veins at the surface very definitely and it was a pleasure to see them.

The response to Dr. von Sallmann's question is partly contained in the closing paragraphs of my paper. Unfortunately, my stay at the Presbyterian Hospital was much too short. I would have liked to discuss all questions more extensively and to go on with more experiments; I think that, like in everything connected with the aqueous veins, there is a lot of information still hiding behind the veil of the future and we have to go on investigating.

With regard to Dr. Pascal's question: we did find patients in the Presbyterian Hospital who could wear their contact lenses for 12 hours. The location of their aqueous veins was very deep, particularly in one man I remember. However, in order to obtain statistically significant evidence, the question should

be approached with a larger material. The responses of aqueous veins to contact lens were the same at reexaminations.

These things are also connected with psychological factors; some people are not much aware of discomfort, others are. This man showed aqueous veins very deeply imbedded in pretty tough subconjunctival tissue; they were not so much on the surface. I do not know whether this will be an explanation in the future.

This will answer partially Dr. McLean's question also. He asked about the number of the aqueous veins. We must bear in mind that those aqueous veins which we see are only a part of the system eliminating aqueous humor and that there are, also connected with Schlemm's canal, other less superficially located veins which we do not easily see; it is possible that eyes which show fewer aqueous veins on the surface will be better wearers of contact lenses because their elimination channels are more protected by scleral and subconjunctival tissue than those with superficially located aqueous veins; but all this is guesswork for the time being. I do not have enough material to give a scientifically valid answer.

To the question of Dr. McLean regarding intraocular pressure: In the beginning I did not compare the intraocular pressure before and after wearing a contact lens. Later, I used the Schiøtz tonometer in every patient over 20 years of age and so I did before insertion and after removal of the contact lens in five or six contact-lens wearers; I did not find any significant differences.

We know that these manipulations influence intraocular pressure; one expresses some intraocular fluid with each application of the tonometer, one lowers the intraocular pressure, but one does not know much about the eye pressure present while the contact lens covers the cornea. Therefore, I would not overestimate this modest contribution concerning the eye-pressure readings.

A CRITICAL STUDY OF LENS METABOLISM*

I. NONENZYMATIC "RESPIRATION"

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Iowa City, Iowa

The maintenance of the structural and functional integrity of the crystalline lens, as well as of other tissues, is dependent on a constant source of metabolic energy. The systems whereby this energy is produced in the lens have been the subject of intense experimental interest during the past several decades—an interest based largely on the implicit connection between variations in this metabolic pattern and the occurrence of anomalies in the lens.

That glucose is consumed by the lens, and that the energy supplying system depends primarily on glucose as substrate has been well demonstrated.¹ It is also well established that an active glycolytic system exists in the lens.^{1, 2} The existence of an oxidative metabolic system, however, has not been established.

Claims for the existence of a respiratory metabolism of the lens are based primarily on the generally observed gas uptake of isolated lenses.^{2, 3} Supporting evidence includes such observations as the action on this gas-uptake reaction of substances, for example cyanide, which are known to act on respiratory enzymes.⁴ There have also been several claims of the demonstration in lens tissue of certain oxidative enzymes,⁵ including parts of the cytochrome system and several dehydrogenases.^{4, 6-9}

On the other hand, several well-established facts point to the absence or relative unimportance of a respiratory system: The essentially anaerobic state of the lens *in situ* where it depends for its oxygen supply on diffusion from the aqueous, a slow process at best and further limited by the low con-

centration of oxygen in the aqueous;¹⁰ the high concentration of reducing substances;^{9, 11} and, finally, conflicting and contradictory evidence as to the occurrence of respiratory enzymes,^{12, 13} particularly negative evidence for the existence in the lens of either succinic dehydrogenase or cytochrome oxidase (or any alternative terminal oxidase).^{8, 12, 14}

The essence of any argument claiming respiratory activity for the lens is the undeniable fact that isolated lenses do take up gas. This gas uptake has been generally attributed to respiration of the lens epithelium, while the bulk substance of the lens has been denied any role or significance in either respiratory activity or this universally observed gas-uptake reaction.^{1-3, 15}

It is a critical study of this gas-uptake reaction of isolated lenses with which these experiments are concerned. In view of the contradictory state of the claims and evidence concerning the nature of this reaction, and in view of other anomalous characteristics, such as its excessively slow rate and its extreme degree of variability, the notion was entertained that the reaction was not an enzymatic one at all but was rather a non-living autoxidation.

This possibility was tested by comparing the rate of gas uptake of lenses, in which all enzymatic activity had been destroyed by protein denaturation, with that of fresh, untreated lenses. The experiments to be described show conclusively that the reaction cannot be catalyzed by a living enzyme system.

Additional experiments show that the reaction is indeed an oxidation; that one mole of oxidative carbon dioxide is produced per mole of oxygen utilized; that the addition of glucose does not influence the reaction; that

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the reaction is not limited to the epithelium but does involve the bulk lens substance; and finally that the reaction is strongly catalyzed by alkali.

EXPERIMENTAL

GENERAL METHODS

These experiments were carried out on either freshly dissected or frozen-thawed lenses. Bovine eyes, obtained from the Wilson Packing Company of Cedar Rapids, were received in the laboratory within five hours after the death of the animal. During this interval the eyes were stored in cracked ice. The lenses were removed and either used immediately in metabolic experiments or were quick frozen and stored at -20°C . for future use.

Rabbit lenses were used immediately after dissection from animals of body weight of 1.0 to 1.5 kg. The rabbits were killed by air injection. Unless otherwise stated, all lenses were whole and the capsule intact. The lenses were weighed fresh at the beginning of the experiment to the nearest two mg. on a torsion balance, and all metabolic activities are expressed on the basis of activity per gram of fresh weight.

Conventional Warburg manometric techniques and apparatus were used for gas ex-

change measurements.¹⁶ The thermostat was maintained at 37.5°C . and the rate of shaking was 120 strokes per minute. Carbon dioxide evolution was determined by the direct method of Warburg, and both CO_2 and O_2 exchange were followed for a period of three hours, with readings at 20-minute intervals. The suspension medium for the O_2 and CO_2 measurements was distilled water, unless otherwise stated.

EFFECT OF FREEZING ON THE O_2 UPTAKE OF BOVINE LENSES.

In order to justify the use of frozen-thawed lenses, it is necessary to determine the effect of this treatment, if any, on the particular reaction being studied. The lenses were removed from fresh bovine eyes; six of these lenses were immediately placed in respirometer flasks and the rate of O_2 uptake measured. The remainder of the lenses were quick frozen and stored at -20°C .

At various time intervals, groups of six lenses were thawed and the rate of gas uptake was measured. The results of such determinations of the effect of storage on the rate of gas uptake are shown in Figure 1.

These data show that the rate of gas uptake of lenses is not affected by freezing and storing for periods up to at least one week. There is some indication of a very slight falling off in rate with longer times of storage, but up to 35 days the magnitude of this decrease is hardly significant.

On the basis of these observations, lenses which had been stored frozen for no longer than one week were considered to be equivalent to fresh lenses with respect to oxygen uptake activity, and were used in these experiments as fresh lenses.

EFFECT OF NUTRIENT MEDIUM ON THE RATE OF O_2 UPTAKE OF LENSES

It is a general observation that the O_2 consumption, in contrast to the glycolytic activity, of lenses is independent of added nutrient.¹⁷ The rate of gas uptake is essentially the same in a medium of pure water,

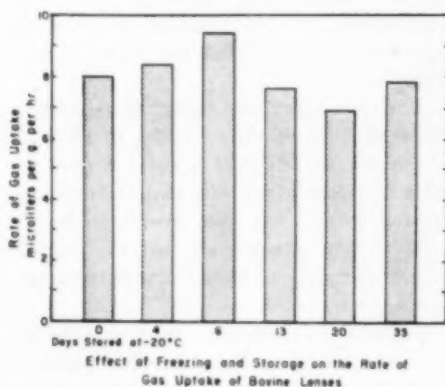


Fig. 1 (Christiansen and Leinfelder). Each bar represents the average rate of gas uptake of six lenses for the three-hour measurement period.

aqueous humor, or a buffered salt-glucose nutrient. Indeed, a dry lens with no added medium at all will take up gas at the same rate as in any nutrient medium used.¹⁸ However, comparison was made, under identical experimental conditions, of the rate of gas uptake in water and in a nutrient made up as follows:

NaCl	0.12 M	CaCl ₂	0.0017 M
KCl	0.0024 M	Glucose	0.011 M
MgCl ₂	0.0007 M	PO ₄ buffer	0.015 M, pH 7.2

This comparison, presented in Table 1, shows clearly that the added nutrient has no beneficial effect on the rate of O₂ uptake of either bovine or rabbit lenses. It can therefore be concluded that the requirements for the oxidation reaction are completely met by the endogenous materials of the lens. Furthermore, the use of distilled water as a medium for the gas exchange experiments, with the accompanying experimental simplifications, is completely justified.

VARIABILITY OF RATE OF O₂ UPTAKE OF BOVINE LENSES

Reported values for the rate of O₂ uptake of lenses of different species show variation as high as tenfold. Even for a single species considerable disagreement of reported rates exists. For example, rabbit lenses are claimed by various authors to respire at rates varying from 20 to 150 μ l. of O₂/gm./hr.¹ Part of this discrepancy can be attributed to variable conditions of measurement. But even in closely controlled experiments a high degree of inherent variation is observed.

TABLE 1
COMPARISON OF RATES OF O₂ UPTAKE OF LENSES
IN WATER AND IN NUTRIENT MEDIUM

	Microliters of O ₂ per gm. per hr.		Number of Determina- tions
	In Water	In Nutrient ¹	
Bovine	8.2	7.8	18
Rabbit	31.5	29.5	9

¹ Nutrient medium composed of the following: 0.12 M NaCl, 0.0024 M KCl, 0.0007 M MgCl₂, 0.0017 M CaCl₂, 0.011 M glucose, 0.015 M PO₄ buffer, pH 7.2.

In the course of these experiments almost 200 separate observations were made of the rate of gas uptake of bovine and rabbit lenses in which the conditions of the experiment were rigidly controlled.

The data from a typical experiment on bovine lenses are shown in Figure 2. The quantitative significance of this single set of data is slight, but the point is demonstrated that straight line relationships result when the gas uptake is plotted against time, showing that a constant rate maintains throughout the three-hour experimental period.

Figure 3 shows the extent of variation and the distribution of the results of the gas uptake determinations on bovine lenses. The number of observations falling within a given range is plotted on the vertical axis against the relative rate of gas uptake on the horizontal axis. These curves have the general outline of probability curves, and show an extreme variation of about fourfold.

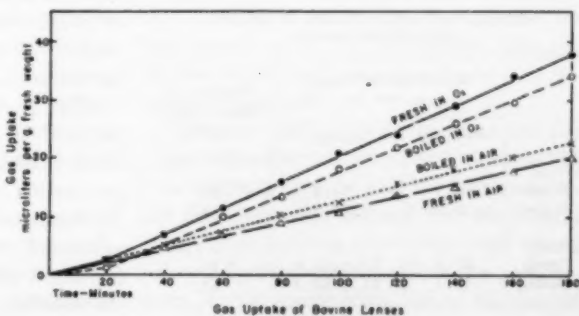


Fig. 2 (Christiansen and Leinfelder). Data typical of all experiments summarized in Table 2 and Figure 3.

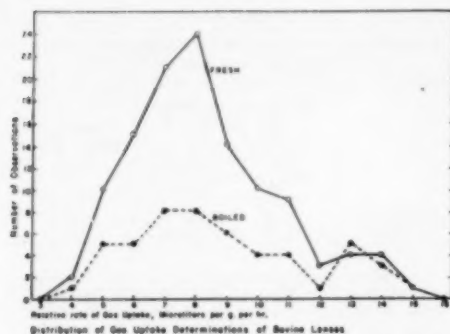


Fig. 3 (Christiansen and Leinfelder). The upper, solid curve refers to fresh lenses, and the broken curve to boiled lenses. All determinations were carried out in an atmosphere of air. Each point represents the number of determinations which fell within a given range of rates. For example, the maximum point of the solid curve indicates that 24 determinations on fresh lenses showed rates of gas uptake between 7 and 8 $\mu\text{l.}/\text{gm.}/\text{hr.}$

Table 2 indicates the degree of variation in the rate of gas uptake of rabbit lenses as well as bovine lenses. Again the range of values is the order of a fourfold variation.

In view of these data it must be accepted that any quantitative conclusions concerning the gas uptake of isolated lenses must be based on a large number of carefully controlled observations.

EFFECT OF ENZYME DENATURATION ON O_2 UPTAKE OF LENSES

(a) *Heat denaturation.* Fresh lenses were placed in Warburg respirometer flasks and

TABLE 2
RATE OF OXYGEN UPTAKE OF FRESH AND BOILED LENSES

	Microliters of O_2 per gm. per hr.		Number of Determinations
	Average	Range	
Bovine:			
Fresh	8.2	3.8-15.8	93
Boiled	8.0	3.5-15.3	53
Rabbit:			
Fresh	31.5	13.1-58.0	14
Boiled	34.7	21.0-58.2	13

covered with two ml. of distilled water. The flasks were then evacuated at the aspirator, flushed with nitrogen, reëvacuated and flushed, and finally plunged into boiling water. The heating was continued for about 10 minutes, at which time the lenses had become a dense, opaque white, and quite hard. The flasks were then cooled in water to room temperature. Throughout the period of heating and cooling a stream of washed nitrogen was passed through the vessels.

After cooling, the flasks were opened, flushed with air, and charged with the necessary ingredients for the particular experiment. Simultaneous determinations were made of the rate of gas uptake of these boiled lenses, and of lenses which had not been heated but which had otherwise been treated the same.

The results of such determinations on a total of 107 fresh and 66 boiled lenses, all in an atmosphere of air, are shown in Table 2. It is apparent that heat denaturation and the concomitant destruction of any oxidative enzyme system have no effect on the rate of gas uptake. This reaction, the uptake of gas by isolated lenses, therefore cannot be an enzymatic respiratory process, but rather must be some nonliving chemical reaction.

(b) *Denaturation with protein precipitants.* Experiments were carried out in which any enzyme systems present in the lens were destroyed by chemical protein precipitants. Reagents used in this way included five-percent trichloroacetic acid, 0.33 M. AlCl_3 , and pure acetone. There is considerable uncertainty as to the degree of enzyme destruction in these treatments since none of these reagents is as effective as heat treatment in denaturation of protein.

All three chemicals caused a surface coagulation of the protein to form a tough, opaque white shell but showed no evidence of deep penetration into the bulk lens substance. Furthermore, the experimental complications associated with the use of these reagents, the direct pH effects of the two acids, and the volatility of the acetone, tend to obscure

effects associated directly with protein denaturation.

Acetone-treated lenses were soaked for 10 minutes in pure acetone, then rinsed briefly in water. The lenses were allowed to equilibrate in the respirometers at 37.5°C. for 30 minutes to remove the acetone and minimize volatilization during the gas exchange measurements. The trichloroacetic acid and AlCl_3 were added directly to the respirometer vessels containing the lenses.

The relative rates of gas uptake, expressed as percent of untreated controls, of lenses treated with these protein denaturants are shown in Figure 4. The small number of experiments preclude any precise quantitative conclusions concerning the effect of these treatments. However, it can be concluded that acetone coagulation of the surface proteins, as with heat destruction, has no effect on the rate of O_2 uptake of lenses.

The two acid denaturants, trichloroacetic acid and AlCl_3 , do cause an undeniable lowering of the rate of gas uptake. This effect is, however, entirely one of pH and is not associated directly with the denaturation of proteins and the inactivation of an enzyme system. The pH of the lenses treated with these substances, as determined by indicators, is below 2 and, as will be shown in a subsequent section of this paper, the gas uptake of lenses is pH sensitive, decreasing in rate with decreasing pH.

EFFECT OF pH ON THE RATE OF GAS UPTAKE OF BOVINE LENSES

The observation that strong acid protein denaturants cause a marked decrease in the rate of gas uptake of lenses, while other methods of protein destruction (including heat and acetone treatment) have no effect, would indicate that the reaction is strongly pH sensitive. Other observations tend to bear out this.

If whole lenses are made basic, a marked rise in the rate of gas uptake is observed. In eight experiments in which 0.2 ml. of 20-percent KOH was dumped, after tempera-

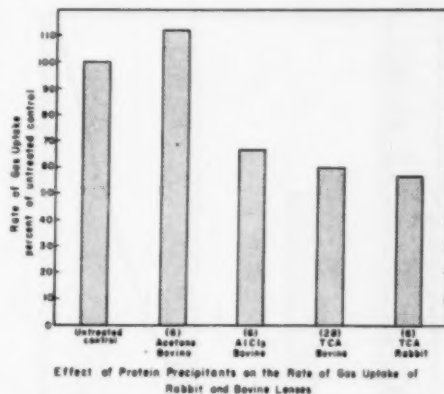


Fig. 4 (Christiansen and Leinfelder). Each bar represents the average rate of gas uptake of the number of lenses and for the treatment indicated under the respective bars. Acetone, 100 percent; AlCl_3 , 0.33 M; trichloroacetic acid (five percent).

ture equilibration, into the body of the respirometer flask containing a bovine lens in 1.0 ml. of water, the rate of O_2 uptake averaged 45 $\mu\text{l.}/\text{gm.}/\text{hr.}$ and ranged from 42 to 49.

The pH of the lens and medium was determined by indicators to be between eight and 10 for each of the eight lenses at the end of the three-hour experiment. Thus a sixfold increase in the rate of O_2 utilization is observed when the pH of the medium rises by about two pH units.

Because of the inherent difficulties in accurately controlling the pH of whole intact lenses, the pH dependence of this reaction was determined on homogenates of lenses. The homogenates were made by grinding frozen bovine lenses with an equal weight of cold distilled water or of buffer solution for two minutes in a Waring blender. The pH of the unbuffered homogenates varied between 6.2 and 6.8.

Phthalate buffers were used for the pH range below 7.0 and borate buffers above, all at a concentration of 0.2 M. Electrometric pH determinations showed that the buffers at this concentration were sufficiently strong to control effectively the pH of the homogenates. In the range from five to 10, the pH

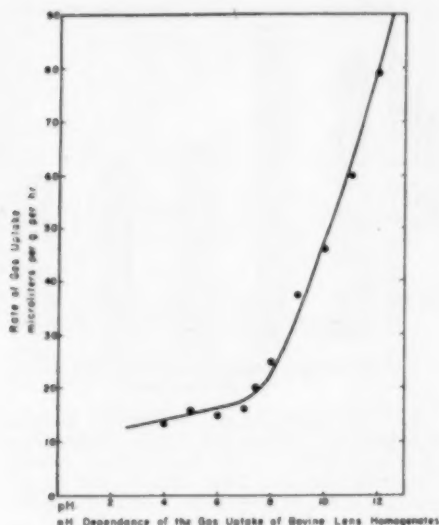


Fig. 5 (Christiansen and Leinfelder). Each point represents the average of two determinations. Frozen lenses were homogenized for two minutes in a Waring blender with equal weight of borate or phthalate buffer, 0.2 M. The pHs were checked with glass-calomel electrodes at the end of the three-hour experimental period.

was not changed at all by the presence of the lens tissue. Beyond this range the change was less than 0.1 pH unit.

The results of these determinations are shown in Figure 5, in which the rate of gas uptake is plotted against the pH. A sharp break in the curve is seen at pH 7.0. Above this point the rate of gas uptake increases rapidly with increasing pH, up to a least 12. Below 7.0 there is a slight decrease in rate with decreasing pH. A curve of this type is characteristic for a chemical reaction, strongly catalyzed by alkali.

The lowering of the rate of O_2 uptake with decreasing pH explains the apparent anticatalytic effect of strong acid protein denaturants described above. The pH of lenses treated with trichloroacetic acid or $AlCl_3$ was below 2.0, and extrapolation of the curve of Figure 5 to this pH indicates that the expected decrease in rate is the same order of magnitude as was observed in the denaturation experiments.

It should also be pointed out that the rate of O_2 consumption per gram of tissue is distinctly greater for homogenates than for whole, intact lenses—about 17 $\mu l./gm./hr.$ for homogenates at pH 6.5 as compared with 8.2 for whole lenses. This observation would be expected if the rate of O_2 uptake is limited by the degree of penetration of O_2 into the whole lens.

EFFECT OF O_2 CONCENTRATION ON THE RATE OF GAS UPTAKE OF LENSES

The reasonable assumption has generally been made that the gas taken up by isolated lenses is in fact oxygen. However, the non-enzymatic character of the reaction, as shown by the denaturation experiments, implies a lack of specificity and suggests that the reaction may be a nonspecific physical uptake of gas. Such a possibility has not been eliminated by previously described experiments.

This possibility was tested by varying the O_2 concentration of the atmosphere in which gas exchange measurements were made. In pure N_2 no measurable gas uptake was observed. This was the invariant result of 18 experiments. Figure 6 shows the effect of pure O_2 on the rate of gas uptake.

In both fresh and boiled lenses the five-fold increase in O_2 concentration, from air to pure O_2 , causes an increase of about 50 percent in the rate of gas uptake. This dependence of the rate of gas uptake on the O_2 concentration, plus the total failure of lenses to take up gas in pure N_2 , proves that the reaction being studied is indeed the consumption of oxygen.

There is a further implication in this increase in rate of O_2 uptake paralleling an increase in the concentration of O_2 . With a thick tissue such as lens, the effect of increasing the concentration of O_2 is to increase the depth to which O_2 penetrates the tissue. Dixon has calculated this to be about 0.5 mm. for pure O_2 as compared with 0.2 mm. for air.¹⁹ Thus we have observed an increase in the rate of O_2 utilization paralleling the penetration to depths beyond 0.2 mm.

This observation suggests that the internal bulk lens substance, as well as the surface epithelium, is involved in the reaction.

EFFECT ON O_2 UPTAKE OF BOVINE LENSES OF REMOVING THE CAPSULE, EPITHELIUM, AND OUTER CORTEX

The gas uptake of isolated lenses *in vitro* has been generally attributed to respiration of the lens epithelium. The observation that denatured lenses still take up oxygen at a rate indistinguishable from undenatured lenses proves that the reaction cannot be a respiratory one in the usual sense of a heat labile enzymatic reaction with oxygen.

Furthermore, the observation that the rate of O_2 consumption increases with increasing depth of penetration of O_2 indicates that the cortex as well as the epithelium is involved in the reaction. This point can be proved, however, by determination of the rate of O_2 consumption by lenses in which the epithelium has been completely removed.

If the reaction is exclusively associated with the epithelium, then such a treatment should remove all or most of the oxidative capacity of the lens.

Frozen bovine lenses were carefully "peeled" to a depth of about one mm. A good deal of the cortex was removed by this treatment, but every trace of the epithelium was assuredly eliminated. The remaining fragment, the nucleus with some cortex, surrounding it, was placed in a respirometer flask, thawed, and the O_2 uptake measured in the usual way.

The rate of O_2 uptake of 10 such nuclear-cortical fragments ranged from 5.9 to 8.3 $\mu\text{l./gm./hr.}$ and averaged 7.3. This, compared with an average of 8.2 for whole, intact, fresh lenses, indicates a decrease in rate of only about 10 percent which, in view of the inherent uncertainties of a small number of observations, is hardly significant.

Thus it must be concluded that the O_2 uptake of isolated lenses is not limited to the surface epithelium, but must involve the bulk lens substance as well.

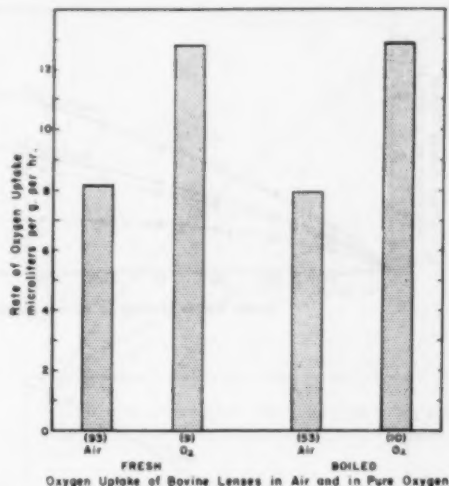


Fig. 6 (Christiansen and Leinfelder). Each bar represents the average of the number of determinations and for the conditions indicated under the respective bars.

CARBON-DIOXIDE PRODUCTION

Carbon-dioxide measurements were made by the direct method of Warburg in atmospheres of air and of pure nitrogen. A typical experiment is shown in Figure 7 and, although the quantitative relationships of a single experiment are of slight significance, several facts are apparent.

First, the rate of CO_2 production is not constant as is the O_2 uptake, but decreases steadily with time. Second, CO_2 is evolved to a considerable extent under anaerobic conditions in which no oxidation can take place. Third, fresh lenses give off CO_2 at a significantly greater rate than do boiled lenses—another point of contrast with the oxidative reaction. And finally, the rate of CO_2 production in air is considerably greater than is the rate of O_2 uptake.

The solid curves of Figures 8, 9, and 10 summarize the data on CO_2 evolution of fresh and boiled bovine lenses and fresh rabbit lenses. Each curve is the plot of the average of the individual readings for all the lenses studied under that particular set of conditions.

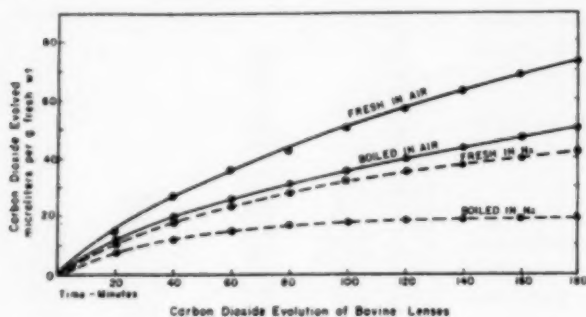


Fig. 7 (Christiansen and Leinfelder). Data typical of all experiments summarized in Figures 8 and 9.

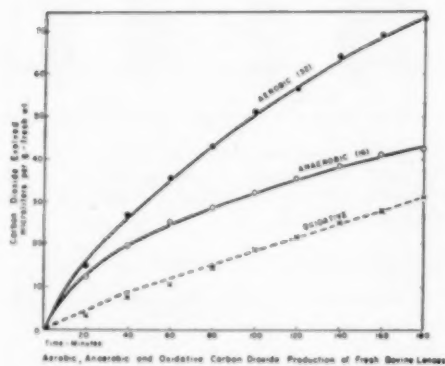


Fig. 8 (Christiansen and Leinfelder). Each point on the aerobic and anaerobic curves represents the average of the individual readings (at 20-minute intervals) for the number of determinations indicated in parentheses on the curve. Aerobic determinations were made in air, anaerobic in nitrogen. The oxidative curve (broken line) was determined by subtracting the anaerobic from the aerobic.

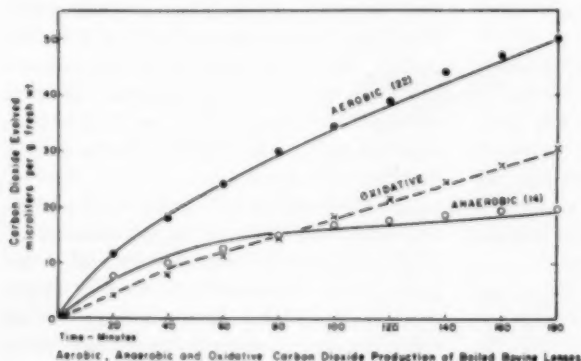


Fig. 9 (Christiansen and Leinfelder). Conditions the same as for Figure 8.

The observation that CO_2 is still evolved, by both fresh and boiled lenses, when maintained in the anaerobic state, shows that at least part of the total CO_2 evolved in air is nonoxidative and must be entirely independent of the oxidation reaction.

There is, however, a considerable production of CO_2 which does accompany and parallel O_2 utilization. This oxidative CO_2 is the difference between the total observed CO_2 evolved in air and that evolved in N_2 , where no oxidation can take place.

The time course of the oxidative CO_2 production, represented by the broken curve in each of Figures 8, 9, and 10, was calculated by subtracting the lower curve (anaerobic CO_2) from the upper curve (aerobic CO_2). In each case a straight line results, indicating a constant rate of oxidative pro-

duction of CO_2 paralleling the constant rate of O_2 consumption. Furthermore, the slopes of these curves, which indicate the rates of oxidative CO_2 production, are extremely close to the corresponding rates of O_2 uptake: 9.2 $\mu\text{l. of CO}_2/\text{gm./hr.}$ compared with 8.2 $\mu\text{l. of O}_2/\text{gm./hr.}$ for fresh bovine lenses, 9.8 to 8.0 for boiled bovine lenses, and 35 to 32 for rabbit lenses.

When expressed as ratios of oxidative CO_2 to O_2 , that is as true respiratory quotients, the values are very close to unity, 1.1, 1.2, and 1.1 respectively. It must be concluded then that the oxidative reaction being studied in these experiments is one in which one mole of CO_2 is produced for each mole of O_2 consumed.

There are two likely sources of this extra, nonoxidative CO_2 : It may be the result of some other chemical reaction, the most probable being the liberation by acid from bicarbonates in the lens tissue; or it may be the physical dissolution of dissolved CO_2 , the gas passing from the state of higher concentration in the lens to lower concentration in the atmosphere.

TOTAL ACID-LIBERATED CO_2 OF BOVINE LENSES

The possibility that the nonoxidative CO_2 evolution may be an acid liberation from bicarbonates of the lens was tested by decomposing these bicarbonates by strong acidification. Sulfuric acid (0.2 ml. of 4 N acid) was dumped from the side arm onto lenses in the body of respirometer flasks at time zero (after temperature equilibration), and at various time intervals throughout the three-hour experimental period.

Such acidification experiments were carried out on fresh and boiled lenses, whole and minced, and in atmospheres of air and of nitrogen. The results of these experiments were essentially the same for all of these conditions. Figure 11 compares the average of 17 fresh lenses in air, acidified at time zero with 32 unacidified controls. Figure 12

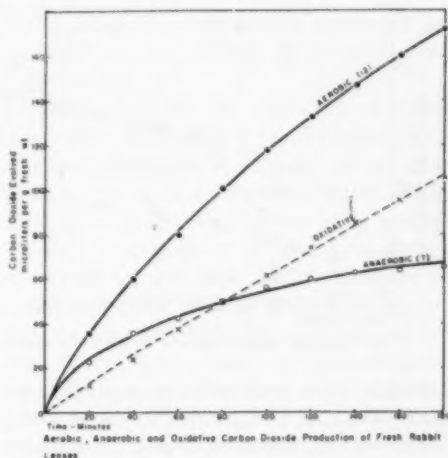


Figure 10 (Christiansen and Leinfelder).
Conditions the same as for Figure 8.

compares eight boiled lenses in nitrogen, acidified in pairs at 40-minute intervals, with 14 unacidified controls.

In these experiments, as well as in those under the other conditions, the effect of strong acidification was a rapid liberation of 20 to 25 $\mu\text{l. of CO}_2$, displacing the acidified curves this amount above the control curves, after which the evolution of CO_2 continued on a course parallel to that of the unacidified controls.

The conclusion is therefore necessary that,

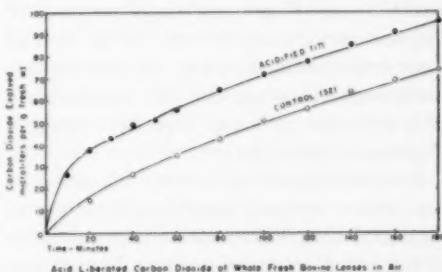


Fig. 11 (Christiansen and Leinfelder). Each curve is the average of the number of determinations shown in parentheses. The lenses were acidified at time zero by dumping 0.2 ml. of 4 N H_2SO_4 into the body of the respirometer flask containing the lens.

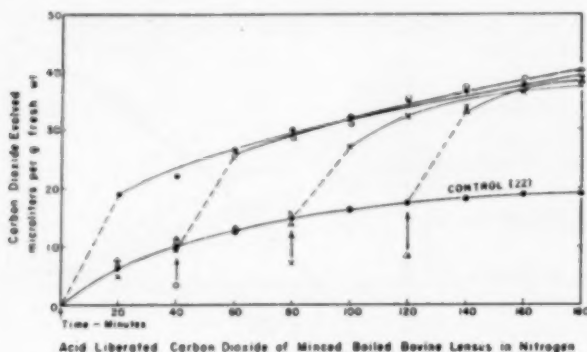


Fig. 12 (Christiansen and Leinfelder). The lower curve represents the average of 22 determinations of the carbon dioxide liberation of boiled lenses. Each of the other curves represents the average of two determinations of acid liberated CO₂. The acid (0.2 ml. of 4 N H₂SO₄) was dumped at the times indicated by the arrows.

although there is bicarbonate equivalent to 20 to 25 μ l. of CO₂ present in the lens, the measured CO₂ evolution of unacidified lenses is entirely independent of any acid decomposition of this bicarbonate to produce CO₂.

EFFECT OF CO₂ CONCENTRATION ON THE EVOLUTION OF CO₂

If the nonoxidative CO₂ evolution represents an approach to solubility equilibrium between the gas phase and the lens, then by the mass action effect the reaction should be prevented or reversed by an increase in the CO₂ concentration of the atmosphere.

Sixteen fresh bovine lenses and eight boiled lenses were studied under conditions identical to those of the already described CO₂ measurements, with the exception that the atmosphere was a mixture of five-percent CO₂ and 95-percent N₂ (a hundredfold increase in CO₂ concentration). In none of these experiments was there measurable gas evolution, indicating that the nonoxidative CO₂ evolution of bovine lenses is a physical dissolution of the gas.

Further supporting evidence is offered by the lower rate and decreased quantity of measured CO₂, both total and nonoxidative, in the boiled lenses, as is shown by comparison of Figures 8 and 9. It would be expected that the repeated evacuation and flushing, as well as the heating, of these lenses would drive off considerable dissolved gas, and thereby decrease the rate and the quantity

evolved during the subsequent observation period.

CONCLUSIONS

The gas uptake of isolated lenses is an oxidation reaction. This conclusion is supported by the observations (a) that no gas is taken up when lenses are incubated in an atmosphere of pure nitrogen, and (b) that increasing the concentration of oxygen in the atmosphere from 20 to 100 percent causes an increase in the rate of gas uptake of about 50 percent.

This oxidative reaction produces one mole of carbon dioxide for each mole of oxygen used. However, the direct relationship between O₂ used and CO₂ produced is obscured in direct carbon-dioxide measurements by a nonoxidative evolution of CO₂ by physical dissolution of gas from the lens to the atmosphere.

This physical dissolution of gas is prevented or reversed by increasing the concentration of CO₂ in the atmosphere. Its magnitude and rate are also lowered appreciably by subjecting the lenses to reduced pressures, and by heating for a short period just prior to the gas exchange measurements.

Increasing the concentration of oxygen in the atmosphere has the effect of increasing the depth to which the gas penetrates the tissue. Thus the observation of an increased rate of oxidation paralleling the increase of O₂ concentration implies that the deeper cor-

tex of the lens as well as the surface epithelium must be involved in the reaction.

Further evidence for this conclusion is contained in the observation that lens homogenates, in which the depth of penetration of the gas is no longer limiting, take up oxygen at twice the rate of whole lenses. That the bulk substance of the lens does indeed participate in this reaction is proven by the fact that removal of all the epithelium (plus the capsule and part of the peripheral cortex) causes no appreciable decrease in the rate of O_2 uptake per weight of tissue.

The major point of these experiments is the inescapable conclusion that the gas uptake of isolated lenses is not a respiratory reaction. This conclusion is based on a total of 116 determinations on fresh lenses compared with 76 on boiled lenses in which no change in the rate of oxygen uptake was caused by boiling.

Such a treatment, in which the lens protein is completely denatured, would be expected, by all normal criteria of protein and enzyme behavior, to destroy completely all enzymatic activity.²⁰ Indeed, the very definition of enzyme includes the concept of heat instability.^{20, 21}

Fortunately, however, there exists, in the presence of an active glycolytic system, a control experiment which obviates the necessity of any assumption as to the degree of enzyme destruction. As will be shown in the second paper of this series,²² the glycolytic activity of isolated lenses is rapidly and completely destroyed by this heat treatment which has no effect on the oxidative reaction.

Supporting evidence for the conclusion that the oxidative reaction of isolated lenses is nonenzymatic is offered by the results of experiments in which the proteins, at least those of the surface, are denatured by chemical precipitants. Acetone treatment which coagulates the surface proteins to a tough, opaque shell does not decrease the rate of O_2 uptake. Strong acids do cause some low-

ering of the rate, but only to the extent expected from the influence of the very markedly lowered pH.

The shape of the pH versus rate of oxidation curve offers further supporting evidence for the nonenzymatic character of the reaction. It is a cardinal characteristic of all enzymatic reactions which have been studied to show a maximum of activity near the center of the pH scale, and to decrease in activity without limit as both extremes of pH are approached.²⁰ The observed pH activity curve is completely atypical of an enzymatic reaction. The slow increase in activity as the pH increases from strong acid to neutrality, then the very rapid, unlimited rise in rate with further increase in pH characterizes the reaction as a chemical oxidation, subject to strong catalysis by alkali.

Finally, the experiments which proved that the noncellular bulk substance of the lense is at least as active as the epithelium in the oxidation reaction should be quoted as still further support of the claim of a non-enzymatic nature of the reaction.

These experiments are by no means the first to demonstrate the presence in the lens of an autoxidizing system. Goldschmidt,²³ Adams,²⁴ and Kronfeld,²⁴ among others, have discussed this question. However, in all of these reports the autoxidizing system was claimed to be a part of or an auxiliary to a hypothetical respiratory metabolism. And in no case was the statement or implication made that it was anything more than an incidental part of or stage in the overall respiration of the crystalline lens. Furthermore, the reaction studied by these investigators was the oxidation of sulfhydryl compounds to disulfides, a reaction which consumes oxygen but produces no CO_2 , and, therefore, cannot be identical to the presently discussed reaction. The relationship, if any, between the two reactions is not clear at present.

These experiments do not answer the question, "Is the epithelium (or any other

part) of the lens capable of carrying out a respiratory metabolism *in vivo*?" However, the implication of these experiments, as well as the mass of previously reported evidence, is that the lens does not respire in the usual sense of a heat labile, enzymatic reaction with oxygen. At most, respiration can be of

only slight importance in the energy metabolism of the lens. These experiments *do* prove that the oxygen uptake of isolated lenses, *in vitro*, is a nonliving, nonenzymatic chemical oxidation of questionable significance in the physiology of the lens.

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A CRITICAL STUDY OF LENS METABOLISM*

II. GLYCOLYSIS

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Energy for the performance of function and the maintenance of structure is derived from respiration and glycolysis. Studies of the metabolism of the lens have demonstrated that glycolytic activity is considerable, but the significance of it seems to have been lost in consideration of the inefficiency of the glycolytic process for energy production. However, the utilization of glucose by the lens and the presence of lactic acid in the aqueous, which is decreased in amount when the lens is removed, indicate that this is a real and active process in maintaining the status of the lens.

Comparisons have shown that the rates of anaerobic and aerobic glycolysis are similar (Kronfeld and Bothman¹), which demonstrates that the process is fully active at all times and adapted to anaerobic conditions. Furthermore, the various stages of glycolysis from the phosphorylation of glucose to the formation of lactic acid have been identified and correlated with the same process occurring in muscle.²

Bellows³ believes that the low oxygen tension of the aqueous indicates that most of the energy requirements of the lens are derived from glycolysis. In cataractous lenses the glycolytic activity is depressed while the oxygen uptake remains unchanged until complete opacity occurs (Campos 1937,⁴ Ferrara 1938,⁵ Talierto, 1939⁶).

Oxygen uptake has been associated with the glutathione oxidation and reduction mechanism (Kronfeld⁷). This seems justified because the "respiratory" activity of the cellular epithelium is the same as that of the acellular cortex.⁸

An investigation was made of the glycolytic process in bovine and rabbit lenses in order to determine its stability and the effects of physical changes upon it.

METHODS

Bovine eyes were obtained from the packing house† where they had been placed in an iced container at 4°C. When received in our laboratory five hours later, the lenses were removed from the eyes and frozen for use in later experiments, lyophilized, or used immediately. The usual weight of the bovine lens was near two gm. Rabbit lenses of near 300 mg. weight were removed from animals weighing 1.0 to 1.5 kg. These were usually utilized immediately, but some were frozen in order to compare them with frozen bovine lenses.

Glycolysis was measured by the manometric technique, whereby CO₂ is liberated from bicarbonate buffer by the lactic acid produced.⁹ Anaerobic methods were used most frequently.

In initial experiments the glycolysis of fresh rabbit and bovine lenses was determined by aerobic and anaerobic methods. These rates demonstrated great variability in activity with individual variations as great as 100 percent or more. Repeated experiments were carried out, and it became apparent that the variability in the two series was the same, and there was no significant difference between the means of the aerobic and the anaerobic series.

Although a correlation appears to exist between the size of the lens (the age of the animal) and the rate of metabolism, the smaller lenses being more active per unit weight than the large ones, a very large number of experiments would have to be done to

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† Wilson & Company, Cedar Rapids, Iowa.

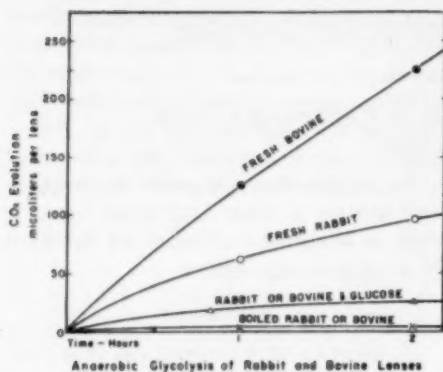


Fig. 1 (Leinfelder and Christiansen). Bovine lenses were approximately 2.0 gm. wet weight; rabbit lenses approximately 0.3 gm.

determine accurately the quantitative relationship.

When one speaks of the rate of glycolysis of the lens, it must be done in relative terms, and one should specify the weight of the lens and the age and species of animal (fig. 1). Even then the values obtained are subject to individual variations.

Rabbit lenses of approximately 500 mg. wet weight usually produce sufficient lactic acid to liberate 5.0 to 6.0 μ l. of CO_2 per 100 mg. per hour, while those near 300 mg. wet

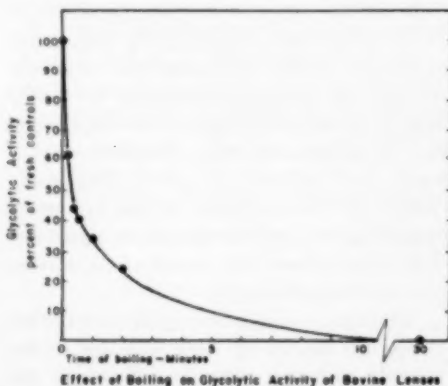


Fig. 2 (Leinfelder and Christiansen). Lenses placed in boiling bicarbonate buffered saline solution for times indicated, then transferred to respirometer flasks and glycolysis measured in the usual way.

weight will liberate 14.0 to 16.0 μ l. per 100 mg. per hour. Bovine lenses of 2.0 gm. are similar in activity to 0.5-gm. rabbit lenses. Sometimes individual lenses will glycolize at two to three times this rate for no recognizable reason.

Glucose in concentration of 200 mg./100 ml. is the ordinary substrate for glycolysis. Its absence from the experimental fluid causes a decided inhibition of glycolysis, but some (lactic) acid production occurs for at least two and one-half hours (fig. 1). The basic rate per mg. per hour without glucose is the same for bovine and rabbit lenses. Liver glycogen and galactose can be utilized by the lens in glycolysis, but with them as substrate the rate of (lactic) acid formation is less than with glucose. The effect of other carbohydrates was not tested.

In order to maintain a supply of experimental material in the laboratory, fresh bovine lenses were quickly frozen and stored at -20°C . Comparison of the glycolysis of these lenses with the fresh demonstrated no apparent difference in activity.

Measurement of glycolysis by lyophilized lenses was technically more difficult because the dehydrated lens material is not hydrophilic, and hydration of all the experimental material was not always accomplished. However, these experiments indicated that (lactic) acid was produced at a rate similar to that of the fresh lens.

Homogenate of bovine lens was made with the Potter-Elvehjem apparatus. This is not a satisfactory method for lenses, since it is very difficult to homogenize completely the tissue. However, the homogenates obtained had a rate of glycolysis comparable to the intact lens. Superior results should be obtained using the Waring blender.

Bovine and rabbit lenses were boiled in bicarbonate buffer saline for varying periods of time (fig. 2). After a two-second immersion, the slightly denatured lenses showed a 35-percent decrease in glycolysis, while boiling for two minutes reduced the activity by 75 percent. More than 10 minutes

of boiling was necessary completely to destroy the glycolytic activity. In one experiment the partially denatured lenses were set up in flasks without glucose substrate, and the same dependence of the residual glycolysis on glucose substrate was observed as occurs with fresh lenses.

The behavior of the glycolytic activity in these experiments indicates clearly that this is a heat labile enzymatic reaction that is not limited to the external layer, but exists in the deep layers of the cortex as well.

When lenses are placed in distilled water containing 200 mg. glucose per 100 ml., glycolysis by the swollen lenses continues at a rate somewhat slower than under usual experimental conditions. When bicarbonate buffer is added to the manometer flask from the side bulb after an hour or more, the initial liberation of CO_2 is followed by continued progressive liberation, but at a rate seemingly less than the controls (fig. 3). Further study is needed to evaluate the relationship between this type of injury to the lens cells and the metabolic activity.

DISCUSSION

These experiments indicate that the lens contains an enzyme system that enables it to convert glucose to (lactic) acid, and that although there is no dependence of the rate upon oxygen tension, the capacity to glycolize is lost by boiling and denaturing the lens protein. Freezing of the lens, or physical disruption of it by lyophilizing or homogenizing, causes little if any change in the glycolytic activity. The dependence of the process upon glucose is demonstrated by the depression in rate that is observed when glucose is not added to the experimental medium. Glycogen is not as satisfactory a nutrient as glucose; this is not unexpected since it is glucose of the aqueous that is the normal substrate for metabolism.

Glycolysis by the lens *in vitro* appears to occur at a fixed rate that is not increased by anaerobic conditions. The low oxygen tension of the aqueous undoubtedly makes it

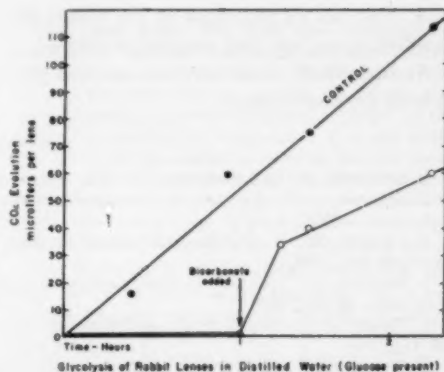


Fig. 3 (Leinfelder and Christiansen). Effect of delayed addition of bicarbonate. Control lenses were in glucose, saline, bicarbonate buffer solution.

unnecessary for the lens to have an inhibiting system that would decrease the rate of glycolysis under aerobic conditions. It seems that the constancy of the system indicates a dependence of the lens metabolism upon glycolysis for energy production.

Denaturation of the lens protein by heat rapidly destroys glycolytic activity. One third of the total glycolysis is lost as the result of dipping the lens in and out of a boiling solution. This suggests that since this amount of activity exists close to the lens capsule, it could be attributed to the metabolism of the lens epithelium. It is possible that following heat treatment the outer layer of denatured protein interferes with the exchange of glucose and lactic acid in the deeper layers of the cortex. However, the same dependence upon glucose is demonstrated by the partially denatured lenses as occurs with the fresh lens. The effects of boiling definitely indicate that a substantial amount of the glycolysis is carried out by the cortical material in the deeper layers of the lens.

CONCLUSIONS

1. Aerobic and anaerobic glycolysis of the lens occurs at the same rate.
2. The glycolytic process of the lens is dependent upon an added substrate (glucose).

3. The rate of glycolysis of the lens is dependent upon age and species of animal.

4. Individual variations in rate of glycolysis are unexplained.

5. Glycolysis of the lens is a heat labile enzymatic process.

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DISCUSSION

DR. JOHN HARRIS (Washington, D.C.): I deem it a privilege to be asked to open the discussion of Dr. Christiansen's paper. I find it very interesting; as always happens, one can go along for some time and have certain things pretty firmly in mind, only to find them questioned by the particularly acute observations of someone else.

There are a couple of things I would like to ask Dr. Christiansen. First of all, whether cyanide will affect this particular system which he described. Secondly, I was wondering whether he can entirely rule out glucose as a substrate in his material. There will be, of course, a certain amount of glucose in the lens. I would like to ask Dr. Christiansen whether he attempted to dialyze the glucose from his boiled lens material and thus prove it was not the substrate utilized.

I think, however, his conclusion that the glycolytic system is the predominant system of importance physiologically in the lens is a very interesting one, and I shall devote the remainder of my discussion to a consideration of certain implications of that conclusion. As you know, the usable energy which comes from any enzymatic system, the glycolytic system, the respiratory system, is usually stored in the form of adenosine triphosphate. As you know, too, the amount of energy produced from the oxidation of one molecule of glucose is considerably greater than the energy derived from the glycolytic breakdown of one molecule of glucose to lactic acid. Thus, if the respiratory system of the lens has no physiologic significance, we certainly are dealing with a rather wasteful mechanism.

This leads to a consideration of the energy needs of the lens. We have a general idea of the uses to which the lens puts its available energy but are unable, at present, to quantitate its requirements. Certainly, the metabolism of the lens is essential for the growth of the lens, for its transparency and

possibly for its elasticity. Just how the available energy maintains the transparency has never been completely answered, although there are many interesting speculations.

Among other things, we attempted to show a year ago that the glycolytic system was essential for the maintenance of a normal cation distribution in the lens and that, in the absence of a normal glycolytic system, the cations tended to shift in the direction of true equilibrium and the lens became intumescent. We anticipated, although it is not shown, that a further event would be a cataract formation.

But there are other and perhaps even more fundamental aspects of the utilization of energy that I think are very interesting. As you know, with the use of radioactive and other means of tagging molecules, it has been shown that any protein is in a constant state of flux. In other words, it is in a constant anabolic and catabolic equilibrium. Amino acids are continuously being split off and are continuously being added; when the lytic process exceeds the synthetic process, we can infer that the metabolic activity of the cell has decreased. I think you can see that the public statement that one has heard so frequently in the past several weeks, that "old soldiers never die, they just fade away," has more of a physiologic significance than the gentleman who voiced it perhaps realized. To maintain a constant state of balance, one needs a continuous energy input.

The lens, then, has definite need of a constant energy supply to maintain such vital functions as growth, transparency and elasticity. We do not know how much energy is required. However, if the respiration of the lens does not contribute, then the lens must derive its needed energy from the breakdown of glucose to lactic acid, and much of the energy potential delivered to the lens is

lost. Yet, this may be essentially the nature of this system. Certainly, the lens has a very poor means of getting oxygen and teleologically, at least, perhaps the system is smarter than we are.

DR. JOHN BELLOWES (Chicago): I believe it is proved in this splendid report that the emphasis that we have heretofore placed on enzymes as being important in the respiration of the lens is not the real factor but that it is purely a temporary reaction of the substrate in the materials and in the lens. I think this is an important step forward in our knowledge of the excitation and the metabolism of the lens.

DR. JAMES S. FRIEDENWALD (Baltimore): Dr. Christiansen's work is, in essence, an amplification of the studies of von Euler of some 15 years ago which led von Euler to the conclusion that there was no respiration in the lens.

About 10 years ago, Dr. Heinz Herrmann in our laboratories made a specific study to find out whether there was any cytochrome oxidase in the lens. Using lens homogenates with cytochrome-C and presenting this mixture with substrates which cytochrome oxidase will oxidize, he was able to show that there was an increased oxygen uptake which was greater than that present in boiled material and which was cyanide sensitive. Consequently, there appears to be evidence of cytochrome oxidase in the lens, however small its total activity may be.

Possibly the discrepancy between Dr. Herrmann's work, and that of von Euler and the present studies of Dr. Christiansen, may be attributed to the relatively low concentration of cytochrome-C in this tissue and the ease with which that low concentration can be diluted to a point where it becomes ineffective in the Warburg type of apparatus. I think it would be interesting, therefore, if these experiments could be repeated with cytochrome-C supplements.

DR. V. EVERETT KINSEY (Detroit): I would like to make several comments concerning the discussion that has gone on thus far. The question has come up of the possible presence of pyruvic acid in the lens. Dr. Charles Frohman and I recently found that pyruvic acid is present in quite measurable quantities in the lens, indicating the existence of an oxidative type of metabolism. The pyruvic acid appears to be concentrated almost exclusively in the epithelial cells. These observations suggest that cytochrome-C does occur in the lens and that it may also be confined to the epithelium. The failure of previous attempts to detect cytochrome-C in the lens may be due to the use of whole lenses rather than lens epithelium. The lens is such a large structure that if most of the cytochrome, if not all of it, is in the epithelium, the dilution effect of including three or four hundred milligrams of lens tissue possibly not containing any cytochrome-C, would reduce the concentration of this compound to levels below those detectable by present methods.

One other point: We have also measured the amount of glucose consumed and the relative amount of lactic acid produced. The amount of lactic acid produced will not account for all the glucose consumed, thus indicating that a portion of the glucose is oxidatively metabolized. I would think it is clear that the oxidation must be brought about by an enzyme system. Dr. Christiansen has presented some very interesting ideas which must be taken into account in further studies evaluating oxygen uptake of the lens.

DR. WILLIAM M. HART (Philadelphia): It has been shown in other tissues that there are many factors affecting the uptake of oxygen. Dr. Baird Hastings, for example, has shown that variation in the electrolyte content of the medium will vary the oxygen uptake of liver tissue by manyfold. Dr. K. A. C. Elliott has shown that varying the electrolyte content of brain tissue will likewise change the rate at which oxygen is taken up.

It is inconceivable that the breakdown of a metabolite can occur by anything other than enzymatic means, since molecular oxygen attacks crude food substances at such extremely low rates.

I have felt for a long time that we put undue emphasis on the quantitative figures which we obtain in a study of oxygen uptake by the lens. It has been said that because the lens sits in an aqueous medium, and since the coefficient of solubility of oxygen in water is so low (the total turnover of water in the eye is 50 cu. mm. per minute as shown by Dr. Cogan and Dr. Kinsey), oxygen must be secreted into the eye. This concept is reminiscent of the pit-fall Dr. Barcroft got into concerning secretion of oxygen by the pulmonary epithelium. It seems more reasonable that the partial pressure of oxygen determines the rate at which the gas is taken up by the lens, as Warburg showed to be the case with some other tissues.

I believe that it is unquestionable that glucose is being used by the lens. Its breakdown must be an enzymatic process in view of the fact that molecular oxygen does not attack this substance. For almost all tissues investigated, the breakdown of carbohydrate occurs through pyruvic acid. It is interesting that no one has satisfactorily demonstrated the presence of pyruvic acid in the lens and, as Dr. Harris has just pointed out, no one has satisfactorily demonstrated a cytochrome system either.

Some years ago Dr. Peters wrote his book on brain metabolism in which it was stressed that methylglyoxal (pyruvic aldehyde) was the intermediate in carbohydrate breakdown. Subsequent work has proved that this is not the case, and the truth was missed because pyruvic acid occurs in such small quantities in the blood that its significance was overlooked. I would pose the question for future consideration whether or not methylglyoxal might be the intermediate in the lens, and I suggest this particularly because we have here the highest concentration of glutathione of any tissue in the body, and the one thing we do know about the function of glutathione is that it is the co-enzyme for glyoxalase. This enzyme catalyzes the break-

down of methylglyoxal to carbon dioxide and water, and is the basis for one of our best methods for the quantitative determination of lactic acid.

If I have misinterpreted any part of Dr. Christiansen's and Dr. Leinfelder's fine paper, I hope they will put me straight.

DR. GORDON S. CHRISTIANSEN (closing): I would like to thank the discussers for their interest in this work. In making reference to the comments, I am sure there is not sufficient time to answer each specifically. However, I feel that one or two general comments are in order.

In the first place, the point of this paper is that the observed gas uptake of isolated lenses is a non-enzymatic reaction. The basis for this statement is the heat stability plus a number of supporting observations, particularly the shape of the pH-activity curve. What I am trying to do, if possible, is to shift the emphasis in the study of the metabolism of the lens (the physiology of the lens as it may apply to the *in vivo* conditions) from this non-enzymatic oxidative reaction to the living enzymatic reactions, such as glycolysis. I feel that this oxygen uptake reaction has slight significance physiologically and is, therefore, a fruitless approach to the study of lens metabolism. The presence or absence of the cytochrome system or other oxidative enzymes makes little difference to this argument. They can only be present in trace quantities, and any oxygen utilization by these systems is overwhelmingly obscured by the nonenzymatic oxygen uptake reaction.

Dr. Harris raised the question of the effect of

inhibitors, particularly cyanide, on this reaction. The effect of inhibitors has not been studied on boiled lenses. However, it is well known that a number of inhibitors, particularly cyanide, inhibit the gas-uptake reaction of fresh, intact lenses. This, of course, does not imply that the reaction must be a respiratory one. It implies nothing beyond the fact that it is perhaps catalyzed by some heavy metal, iron or copper being the two most likely metals.

This brings up a question raised by Dr. Hart. If I understand Dr. Hart correctly, he made the statement or implication that substrates cannot act directly with oxygen. This, I believe, is not true. A great number of substances, for example pyruvic acid and even glucose at alkaline pH, can do so. Two particularly good examples are the sulfhydryl compounds such as glutathione and ascorbic acid, both of which are present in large concentrations in the lens, and both of which, in the presence of traces of copper (which of course are present in the lens), carry out an extremely rapid reaction with molecular oxygen.

An incidental point that may be of interest here is that, in absolutely pure distilled water from which all copper has been completely removed (and this means those concentrations present in glass distilled water), if the pH rises above 7.2, the reaction of ascorbic acid with oxygen is extremely rapid, and by the time it reaches pH 10, the reaction is essentially instantaneous.

I think these comments cover the particular points in which I was interested. I wish to thank again the discussers for their interest in this work.

THE CHEMICAL DEMONSTRATION OF TRANSCONJUNCTIVAL PASSAGE OF AQUEOUS AFTER ANTIGLAUCOMATOUS OPERATIONS*

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Sclerotomies, sclerectomies, and iridencleises near the limbus lead, in a high percentage of cases, to the establishment of a sclerostomy (Verhoeff¹); that is, a permanent macroscopic communication between the anterior chamber and the subtenonian or subconjunctival space.

From there, clinical and biomicroscopic observations suggest, aqueous spreads within the epibulbar tissues and is absorbed in the same manner as accumulations of extra-

cellular fluid elsewhere in the body. In the case of intraconjunctival fluid accumulations there is the additional possibility of elimination by passage through the conjunctival surface into the cul-de-sac.

Both processes of aqueous disposal are associated with characteristic transformation of the tissues exposed to it. The transformation leads to the clinical appearances commonly referred to as blebs.

Suggestive of transconjunctival passage of aqueous are thin-surfaced, transparent, polycystic, vesicular areas which may be surrounded by or interspersed with solid opaque

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areas. Whether entirely polycystic or partly solid, the bleb is usually well circumscribed and sharply set off against the normal, untransformed, surrounding conjunctiva.

For the clinical demonstration of the transconjunctival mode of aqueous elimination Seidel² devised his fluorescein test which, in gross cases, gives a very striking and unequivocal evidence of such transconjunctival fluid passage. Seidel went one step further and determined the amount of fluid elimination through a bleb by means of a small cotton roll placed against the bleb for several minutes, using other, unoperated portions of the limbus as control. In one such case he arrived at a figure of two cu. mm. per minute.

Not infrequently cases are encountered in which the biomicroscopic examination of the area of operation suggests transconjunctival passage in the face of indefinite, equivocal results of the Seidel test. The purpose of this paper was to determine whether the transconjunctival passage of aqueous could be demonstrated more accurately and perhaps quantitatively by chemical means.

It appeared probable that the high ascorbic-acid content of the aqueous would serve to identify this fluid in the contents of the conjunctival sac. To test this possibility the ascorbic-acid content was determined in the contents of the conjunctival sac of patients showing the type of bleb mentioned in the foregoing and in suitable control cases.

METHODS

Samples of the contents of the conjunctival sac were obtained with filter paper discs, five mm. in diameter, mounted on platinum wire for the purpose of easier handling and weighing. After trying various types of paper, Whatman's filter paper No. 50, hardened and acid washed, was chosen. The individual paper discs plus platinum wire were weighed and stored in weighing bottles.

Immediately after "picking up" portions of the contents of the conjunctival sac (see below) the paper discs plus wire were weighed again and placed in the depressions

of an ice-cold, white-porcelain spot plate containing 0.2 ml. of 2.5-percent freshly prepared metaphosphoric acid. The samples were titrated with sodium 2,6-dichlorophenol-indophenol out of microburettes graduated to allow readings of 0.002 ml. and estimates of 0.0002 ml. All titrations were done within two hours of the withdrawal time. The results were considered to represent ascorbic acid.

Samples were obtained from several typical locations of the conjunctival sac, invariably under local anesthesia produced by three instillations of 0.5-percent pontocaine, two minutes apart.

Tears were obtained from the outer fornix, carefully dipping one edge of the filter paper disc into the gross accumulation of fluid usually present in this region. Care was taken not to establish contact with any part of the conjunctiva. If such contact occurred, the conjunctiva would tend to cling to the paper disc and become displaced with it for a distance of three to four mm., at which point it would usually break away from the paper. The amounts of ascorbic acid picked up under contact conditions were invariably higher than without such contact.

Other samples of tears were obtained by dipping the edge of the filter paper disc into the inferior marginal strip. No consistent differences in ascorbic acid content were encountered between tears obtained from these two sources, that is the outer fornix and the inferior marginal strip.

Fluid from the bleb area was obtained by gently touching and mopping the area of the bleb with either the edge or the flat surface of the paper disc. Because of the fineness and flexibility of the platinum wire on which the discs were mounted (36 gauge), the operator did not completely control the part of the disc that established contact with the bleb surface. Special care was taken to keep the wire from touching or rubbing against any part of the surface of the bleb. In most cases, if the bleb was of the type described before, its surface did not show any tendency

to follow the paper disc upon the latter's withdrawal. The reason for this seemed to be mostly the persistent moistness of the bleb surface.

The bleb area was examined microscopically, with or without fluorescein, before and after withdrawal of the aqueous. No consistent or significant alterations in the appearance of the bleb, attributable to the procedure of withdrawal, could be seen. The depth of the anterior chamber was measured a number of times before and after withdrawal and no significant differences were noted.

In order to have samples of the normal contents of the conjunctival sac that could serve as controls for the fluid presumably escaping through the bleb, filter paper discs were applied to the upper bulbar conjunctiva of unoperated human eyes in the manner described under the heading of bleb fluid, that is with a gentle mopping motion. Invariably the conjunctiva stuck to the paper and was lifted up two to three mm. before breaking away.

Performed on the same area of bulbar conjunctiva eight to 10 times in fairly rapid succession, this mopping usually yielded slight partial moistening of the paper and a gain in weight amounting to 0.0003 to 0.0005 gm. The area thus treated appeared dry immediately after the paper disc was removed but regained its moistness and luster after one or two blinking movements.

To determine more closely the nature of material obtained by this method, samples of it were examined under the microscope with and without staining with methylene blue or Wright's stain and found to contain epithelial cells in greatly varying amounts.

At each sitting from three to eight successive samples were obtained from each location in the conjunctival sac. Between the withdrawals the patient was advised to blink naturally. The amounts of fluid obtained by this method varied depending primarily upon the location. Dipped into the outer fornix of most of the eyes tested the filter-paper

disc could be seen to wet very rapidly to an apparent saturation point. Applied to the bleb surface, the wetting took place with perceptibly lower speed than in the outer fornix.

Each eye tested seemed to be characterized by its own wetting speed which to some extent varied from one time to the next. Applied to the upper bulbar conjunctiva of unoperated eyes, the wetting took place very slowly and sometimes invisibly so that only the weighing process indicated that some material had been picked up. In other instances a very slow and slight wetting of parts of filter paper could be seen.

The magnitude of some of the experimental errors entailed in these ascorbic-acid determinations may be estimated from experiments in which known ascorbic-acid solutions were treated as described under tears (table 1). In addition to the sources of error comprised in this determination there was the possibility of the various components of the contents of the conjunctival sac contaminating each other.

In some of the tests, herein reported, this contamination was reduced to a minimum by the prevention of blinking during and between withdrawals and by discarding the first, presumably mixed sample. Samples obtained in this manner were probably chemically purer but less physiologic than the samples obtained by the ordinary method.

RESULTS AND COMMENTS

The findings in the fluid from bleb areas are exemplified by Case 3031 shown in Tables 2 and 3.

M. E. H., a white woman, aged 69 years, glaucoma clinic No. 3031, had been operated on for chronic glaucoma at another institution two years before her visit to the glaucoma clinic of the Illinois Eye and Ear Infirmary (May 18, 1949). The operations could be recognized as corneoscleral trephinations which had caused lowering of the ocular tension to below 10 mm. Hg (Schiötz) and large vesicular thin-walled blebs.

TABLE 1
YIELD AND ACCURACY OF ASCORBIC-ACID ANALYSES BY THE FILTER-PAPER DISC METHOD

Ascorbic Acid (mg. %)												
Theoretically Available	Obtained (Individual filter-paper discs)											Mean
	5.6	5.8	6.1	4.6	5.0	6.0						
5	5.6	5.8	6.1	4.6	5.0	6.0						5.5
10	8.6	9.7	10.1	11.0	11.0	11.3						10.3
10	9.7	10.0	12.4	9.7	9.7	11.4	10.6	9.7	9.1	9.3	9.8	10.17

TABLE 2
AMOUNTS OF FLUID OBTAINED FROM THE BLEB AREA OF THE LEFT EYE OF CASE 3031

Date of Withdrawal	Amounts of Fluid Obtained (mg.)							
	1	2	3	4	5	6	7	8
1-17-51	1.2	1.0	1.0					
2- 2-51	0.6	0.6	0.7					
2-10-51	0.6	0.4	0.6	0.5	0.4			
2-14-51	2.2	1.1	1.1	1.5	1.7	1.1		
2-17-51	2.4	1.0	2.2	0.9	1.5	1.6	0.8	0.7
2-21-51	0.6	0.9	0.4	0.7	0.7			

During a two-year period of observation the visual functions of each eye remained stationary. The result of the Seidel test varied from strikingly positive on some occasions to indefinite or negative at other occasions. Tonography after Grant³ revealed, for the left eye, a coefficient of outflow varying from 0.4 to 0.5, considerably in excess of the normal average.

Each time a filter paper disc was applied to the bleb area of Case 3031 the presence of free fluid manifested itself by immediate wetting of the portion of the paper in contact with the bleb surface. This wetting increased visibly during the mopping motions so that, after about 10 seconds, most or all of the disc appeared moist. When the next dry paper disc was applied about 15 seconds later, the wetting again started immediately and continued at more or less the same rate as in the case of the previous paper disc. Thus, the continuous appearance of fluid on the surface of the bleb could actually be observed.

The weights of the fluids picked up with single discs in the manner already described

are shown in Table 2. Although the method of obtaining fluid from the bleb surface could not be considered quantitative in the sense of comprising all the fluid appearing on the bleb surface per time unit, the figures of Table 2 may be taken to be roughly related to the total rate of fluid production and the conclusion may be drawn that this rate is relatively steady during each test but varies considerably on different days.

Turning to the ascorbic-acid content of

TABLE 3
THE ASCORBIC-ACID CONTENT OF TEARS AND BLEB FLUID FROM THE LEFT EYE OF CASE 3031

(Each figure represents the average of from three to eight consecutive samples.)

Date of Withdrawal	Ascorbic-acid Content (mg. %)	
	Tears	Aqueous
1-17-51	3.6	26.8
2- 2-51	2.9	33.0
2-10-51	4.82	31.4
2-14-51	3.8	26.2
2-17-52	1.3	22.6
2-21-51	3.8	29.8

the bleb fluid, Table 3 lists the ascorbic-acid averages of the samples whose weights were given in Table 2. The ascorbic acid combined average is 22.6 mg. percent, with from day to day variations of ± 20 percent. Considering the experimental error inherent in determinations of this kind, the combined findings of Tables 2 and 3 suggest that a fluid of relatively high and fairly constant ascorbic-acid content makes its appearance on the bleb surface at a fairly steady rate.

The question arose whether any of the constituents of the conjunctival secretion could account for this bleb fluid. While markedly different from the bleb fluid in Case 3031, the tears contained a surprisingly large amount ascorbic-acid, strikingly in excess of the ascorbic-acid content of the blood. This called for more systematic study which is reported here only in part.

On 20 patients admitted to the Illinois Eye and Ear Infirmary for the removal of cataract the ascorbic acid of the tears was determined on both eyes. The results showed variations within the limits of 0 and 13.99 mg. percent, with the relative frequencies shown in Table 4 and without any apparent relationship to the ascorbic-acid content of the serum. In 80 percent of the eyes the ascorbic-acid content of the tears was less than 6.0 mg. percent.

The direct comparison of the ascorbic-acid content in tears and bleb fluid in 12 eyes operated on for chronic glaucoma (table 5) shows that, in all but one instance, the ascorbic-acid contents of the two fluids were so markedly different as to make them easily distinguishable from each other. In all the cases listed in Table 5, the upper lid ordinarily

covered the entire bleb area so that evaporation could not have affected the bleb fluid significantly.

It, therefore, appears highly improbable that the bleb fluid is in any way derived from tears. Bleb fluid may, however, become contaminated with tears if, during the procedure of withdrawal, reflex tearing is set up as a result of the local anesthesia wearing off. The return of the patient's sensitivity and the unusual flow of tears was plainly visible in such cases and could account for some of the last one or two samples showing a very much lower ascorbic acid content than the first three or four.

While tears can be excluded as a source of the bleb fluid, there was encountered in this study another type of fluid that proved rather difficult to distinguish from bleb fluid. As stated under the description of methods, application of the filter paper discs to the upper bulbar conjunctiva in the usual mopping manner yielded in most cases small amounts of fluid.

The ascorbic-acid content of that fluid was rather inconstant but usually within the range of 20 to 45 mg. percent, that is distinctly different from tears and in the neighborhood or in excess of the ascorbic-acid content of the bleb fluid. With regard to the nature of this fluid obtained from the upper bulbar conjunctiva the following observations may be pertinent:

1. In cases in which very small amounts of fluid were obtained, amounts weighing 0.0001 or 0.0002 gm., the ascorbic-acid content was usually very high and microscopic examination revealed solid formations of epithelial cells.

TABLE 4
THE ASCORBIC-ACID CONTENT OF THE TEARS
(In mg. percent; relative frequencies in percent.)

0-1.99	2.00-3.99	4.00-5.99	6.00-7.99	8.00-9.99	10.00-11.99	12.00-13.99
5	35	42.5	5	2.5	5	5

2. In specimens weighing from 0.0003 to 0.0007 gm., the ascorbic-acid content varied within the limits stated before (20 and 45 mg. percent) and the cell count was small. Only an occasional single cell or a few clusters could be seen.

3. This fluid reformed if the patient was allowed to blink once or twice between withdrawals. If the patient was not allowed to blink and if a second paper disc was applied to the area from which fluid containing from 20 to 45 mg. percent had just been removed, the second filter disc yielded only very little weight, a very high ascorbic-acid content, and again an overabundance of cells.

The interpretation of these observations probably should be that, ordinarily, a filter-paper disc applied to the upper bulbar conjunctiva picks up a fluid film, perhaps the equivalent of the precorneal film plus a varying number of cells. The film reforms with every blinking motion. If this is prevented, the epithelium is exposed to the filter paper without any lubricant, is sucked right into the filter paper and largely removed with it. The high ascorbic-acid content of the epithelial cells of the conjunctiva is in line with the findings of Henkes⁴ in the epithelium of the cornea.

Since the ascorbic-acid content of the fluid from the upper bulbar conjunctiva is in the same general range as that of the bleb fluid, the distinction between the two fluids required special methods.

One way of distinguishing between the two fluids was to prevent regeneration of the fluid film covering the upper bulbar conjunctiva by avoiding contact with the upper lid. Under those conditions the ascorbic-acid content of all subsequent specimens obtained from the upper bulbar conjunctiva, containing chiefly epithelial cells, rose to and remained in the neighborhood of 100 mg. percent, while the ascorbic-acid content of the bleb fluid stayed at its usual level.

Another way of distinguishing between

TABLE 5
AVERAGES OF FROM FIVE TO 15 DETERMINATIONS
OF THE TEARS AND BLEB FLUIDS IN
12 DIFFERENT EYES

Case Number	Ascorbic-acid Content (mg. %)	
	Tears	Bleb Fluid
3031, left	3.1	22.6
1448, left	6.7	23.5
3217, left	2.6	14.8
2926, right	3.7	22.6
1758, right	8.0	20.2
left	3.5	22.6
1564, right	3.0	17.5
2706, right	4.1	14.2
2847, right	5.3	20.0
left	5.5	17.5
E.M., right	3.6	26.4
left	6.2	25.2

the two fluids was offered in patients who had been operated in one eye only and whose bulbar conjunctiva of the other eye could serve as control. In most of those instances, the fluid film from the bulbar conjunctiva had a somewhat higher ascorbic-acid content than the bleb fluid from the opposite eye (table 6).

Finally, the bleb fluid could be demon-

TABLE 6
COMPARISON BETWEEN THE BLEB FLUID FROM THE
OPERATED EYE AND THE FLUID FILM OVER THE BUL-
BAR CONJUNCTIVA IN THE UNOPERATED EYE

Case Number	Ascorbic-acid content (mg. %)	
	Bleb Fluid Operated Eye	Bulbar Conjunctiva Unoperated Eye
768	12.0	31.9
	13.7	23.5
	13.0	31.8
	15.2	26.0
1564	16.8	30.6
	16.9	24.3
	18.8	35.6
3217	15.7	38.2
	18.2	34.2
	10.4	—
2706	12.6	—
	17.4	30.6
	13.0	30.6

TABLE 7

RELATIONSHIP BETWEEN OCULAR TENSION, COEFFICIENT OF OUTFLOW AND AMOUNTS OF FLUID ON THE BLEB SURFACE WITH AND WITHOUT EXTERNAL PRESSURE (Case 2847)

Eye	Tension Range	Coefficient of Outflow	Amount of Bleb Fluid (mg.)							
			At the Prevailing Ocular Tension				Under Pressure			
R	10-20	0.16-0.17	2.0	1.7	1.7	1.7	2.1	3.3	2.6	1.7
L	14-25	0.13-0.15	0.5	0.2	0.2	0.3	0.7	1.0	1.2	0.9

strated as having originated from the bleb by a quantitative relationship with the ocular tension. This is exemplified in Case 2847.

J. D., a Negro, aged 65 years, glaucoma clinic No. 2847, at his first visit to the outpatient department of the Illinois Eye and Ear Infirmary, was found to be affected with advanced chronic (open-angle) glaucoma for the relief of which iridencleises were performed on both eyes during August, 1948.

Well-circumscribed, partly thin-walled and polycystic blebs formed in both eyes, the thin-walled portion being considerably larger in the right than in the left eye. The ocular tension became normalized in both eyes, at a slightly but consistently higher level in the left than in the right eye (table 5). The coefficient of outflow varied from 0.16 to 0.17 in the right and from 0.13 to 0.15 in the left eye.

Table 7 shows the amounts of fluid picked by the usual procedure and, immediately following, under the effect of external pressure against the lower sclera (Kronfeld and McGarry³), raising the ocular tension to a level between 25 and 30 mm. Hg (Schiotz). The amounts of fluid available on the bleb surface were distinctly higher in the eye with the lower ocular tension and increased sharply with the application of pressure. Ascorbic-acid determinations during the procedure indicated the appearance on the bleb surface of a fluid of fairly constant composition.

In the whole group of eyes with partly

thin-walled polycystic blebs, there was no definite correlation between the amounts of bleb fluid picked up and the prevailing ocular tension. The lack of such a correlation is probably due to the inaccuracy both of methods of measurement and tonometry as well as to the collection of the bleb fluid. Different rates of fluid, that is aqueous, formation may also have been a factor.

Needless to say, all the observations reported here can be expected to apply only to the thin-walled, polycystic blebs.

SUMMARY

The evidence presented herein suggests:

1. That the fluid which makes its appearance on the conjunctival surface of thin-walled, polycystic blebs after trephination or iris-inclusion operations is not derived from tears or other conjunctival secretions.

2. That this fluid under ordinary conditions makes its appearance at a fairly steady rate and that this rate is distinctly increased by a rise in ocular tension produced by external pressure.

3. That this fluid most likely represents aqueous.

4. That fluid samples obtained in this manner may be used to determine the effects of pharmacologic and pathologic agents upon the composition of the aqueous.

109 North Wabash Avenue (2).

The technical assistance of Miss Thelma Dailey is gratefully acknowledged.

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DISCUSSION

DR. HAROLD G. SCHEIE [Philadelphia]: Dr. Kronfeld's very interesting and highly original paper serves, I believe, first of all to emphasize our lack of understanding of the mechanism by which our various approaches to the treatment of glaucoma lower ocular tension. Neither the effect of miotics nor the action of various surgical procedures has been adequately explained.

As you all know, such outstanding authorities as Duke-Elder and Weckers insist that filtration procedures do not work as such, but lower the ocular tension by altering the axone-reflex mechanism of the uveal tract. Dr. Kronfeld and others, including myself, believe, on the other hand, that these operations act in a mechanical way and allow subconjunctival drainage of aqueous, thereby lowering the ocular tension.

The present paper is, therefore, of importance because it offers further evidence to support the filtration theory. Dr. Kronfeld has produced evidence by his filter-paper test, as well as chemically, to suggest that aqueous drains not only into the subconjunctival space but also through the conjunctiva covering the bleb.

There are one or two questions I should like to ask Dr. Kronfeld. Not having read his paper beforehand, possibly I did not understand clearly. He did not find an increased amount of aqueous on flap types of scars, while he did in polycystic elevated blebs. I wonder if, possibly, this could not be explained by an accumulation of lacrimal fluid in the crevices and clefts of the polycystic scars, which the filter paper might blot up.

The other point that worried me, and again I may not have understood, was that tests made at the limbus of normal eyes showed high concentrations of ascorbic acid, a fact which might indicate escape of this substance through the normal limbus and would therefore not necessarily serve as evidence of filtration through the bleb. The fact that larger amounts of aqueous were absorbed by the filter paper under conditions of increased ocular pressure seems more convincing of escape of fluid through the conjunctival covering of the bleb.

It appears likely that Dr. Kronfeld has made an excellent start toward contributing knowledge of the mechanism of filtering operations comparable to

his work upon the function of the canal of Schlemm.

DR. PETER C. KRONFELD (closing): I believe Dr. Scheie has a very good point in asking whether there was any difference between, on the one hand, blebs that had a smooth surface without any crevices and, on the other hand, blebs with multiple crevices in which fluid could stagnate and conceivably become more concentrated by evaporation.

Most of our findings were obtained on blebs the surface of which was distinctly convex without valleys or grooves. The blebs of which I showed pictures were of that pattern. The thin-walled portion had a vesicular convex surface and it is on that surface, I believe, that the bleb fluid made its appearance.

The normal fluid from the bulbar conjunctiva worried us a great deal and for a while we thought there just was no way of distinguishing between that normal fluid which has a remarkably high ascorbic-acid content, and the bleb fluid. Not until we discovered the method of preventing regeneration of the normal fluid from the bulbar conjunctiva did we become satisfied that there were two distinguishable fluids.

If I may repeat—the upper bulbar conjunctiva is covered by small amounts of fluid that contains from 20 to 45 mg. percent of ascorbic acid. This fluid should probably be called preconjunctival fluid, a rather elaborately constructed fluid film to which the small conjunctival glands probably contribute materially.

If a sample of this fluid is withdrawn and the lid allowed to come down a number of times, more samples of the same fluid can be obtained. If regeneration of this fluid is prevented by keeping the lid up, then a second or third sample will show a sky-high ascorbic-acid content, 125 mg. percent or more, and the microscopic examination reveals just epithelial cells.

I think this indicates that bulbar-conjunctival fluid is regenerated by the movement of the lid. Bleb fluid, on the other hand, is entirely independent of that movement and keeps regenerating whether the lid is allowed to come down and whether the lid is retracted.

AN EVALUATION OF THE VARIOUS ANTICHOLINESTERASE AGENTS*

JAY G. LINN, JR., M.D., AND RAYMOND C. TOMARELLI, M.D.
Pittsburgh, Pennsylvania

The present study was made to compare the effects of the various anticholinesterase agents on the normal eye. All of the drugs used in the experiments are similar in action in that they block the action of cholinesterase.

Leopold and Comroe¹ compared the effects of five-percent neostigmine bromide (pro-stigmine) and one-percent di-isopropyl fluorophosphate (DFP). The concentration of DFP used in their studies was much stronger than that used in the treatment of glaucoma.

Grant² determined the minimal concentration of physostigmine salicylate, DFP, and tetraethyl pyrophosphate (TEP) which would produce a perceptible miotic effect. These concentrations were much weaker than those used clinically. Kull³ compared neostigmine bromide and physostigmine salicylate but focused her attention on the effects on the intraocular pressure.

In this study, we have compared all of the anticholinesterase agents available today, three of which are commonly used in glaucoma therapy. An attempt was made to use a concentration of each drug corresponding to the strongest concentration which might be prescribed in the treatment of glaucoma.

Five different anticholinesterase agents were compared. One-percent physostigmine salicylate, five-percent neostigmine bromide, and eight-percent stigmatene bromide (1 benzyl 3(dimethylcarbamoyloxy) pyridinium bromide) were used in an aqueous solution; 0.1-percent di-isopropyl fluorophosphate

(DFP) and 0.1-percent tetraethyl pyrophosphate (TEP) were dissolved in peanut oil.

Stigmatene bromide has been used systemically for abdominal distention⁴ but has never been used locally in the eye. The concentration of stigmatene producing maximal miosis without undue ocular irritation was determined on rabbits. An eight-percent solution was found to be most satisfactory.

In our studies, we have been concerned primarily with the rapidity and duration of miosis obtained in the normal eye with a single ocular instillation of each drug. A series of rabbit experiments were also made to determine the ability of each cholinergic drug to overcome atropine. Signs of local irritation and the effect on the intraocular pressure of the normal eye were recorded.

RABBIT EXPERIMENTS

A preliminary evaluation of these cholinergic drugs was made on rabbits. The results of these experiments were reported in detail at a previous meeting[†] and only pertinent points will be mentioned at this time. These drugs produced a miosis in the rabbit eye which was maintained for a much shorter period of time than that of human eyes. Only with DFP was any miosis evident after 24 hours and this lasted less than 48 hours. Neostigmine was found to be more effective in the rabbit eye than in the human eye when compared with the other anticholinesterase agents.

The ability of these various drugs to overcome atropine was tested in rabbits in a second series of experiments. Jackson⁵ made an extensive study of the ability of physostigmine to overcome atropine in rabbit and human eyes. Leopold and Comroe¹ noted the ability of DFP to overcome atropine.

[†] Second annual meeting of the East Central Section of the Association for Research in Ophthalmology, January, 1951, at Cincinnati, Ohio.

* From the Department of Ophthalmology and the Addison H. Gibson Laboratory of the University of Pittsburgh School of Medicine. This study was supported in part by a grant from the Ophthalmic Foundation of Pittsburgh. The stigmatene bromide was supplied by the William R. Warner Company, New York. The tetraethyl pyrophosphate was supplied by Eli Lilly and Company, Indianapolis.

In both papers, an antagonism of the anticholinesterase agent for atropine was suggested. This would be a new concept in pharmacology since atropine has been considered to block the effect of acetylcholine or any similar acting agent on the effector organ. The anticholinesterase agents have been thought merely to prevent the destruction of acetylcholine by cholinesterase thereby permitting a building-up of acetylcholine at the effector organ.

If the action of acetylcholine is blocked completely by atropine, the increased amount present could not possibly produce any effector response. Therefore, if atropinization is complete, we should expect to find a dilated pupil entirely unresponsive to any anticholinesterase agent.

If the atropinization is incomplete, there may be a response. The degree of response would depend on three variables: (1) The relative potency of the anticholinesterase agent being tested, (2) the frequency of instillation of the agent, and (3) the actual degree of atropinization.

In one series of experiments, a solution of three-percent atropine sulfate was instilled in one eye of each rabbit three times on the preceding day. Before beginning the experiment, it was noted each time that the pupils of some rabbits reacted slightly to light. A repeat of the preliminary medication and careful control to see that the atropine was properly instilled failed to correct this discrepancy. It was concluded that the action of atropine like that of the miotics was of shorter duration in rabbits.

An instillation of the miotic being tested was made every 10 minutes for two hours after the above preliminary medication. In all series of rabbits (10 or more in a series) and with each anticholinesterase agent, there was an average reduction of pupil size to a point slightly smaller than that of the control eye in which no medication had been used.

The average pupil size in each group followed a similar curve with each miotic. In

no group was maximal miosis obtained. There was, however, a marked variation of pupil size among the several animals in each group. In many instances pupils varied five mm. in size.

It was concluded that we had demonstrated a variable degree of atropinization among individual animals but no difference in ability of the various cholinergic drugs to exert an effect antagonistic to atropine.

In view of the apparently short duration of action of atropine in rabbits, a second group of experiments was performed. Three-percent atropine-sulfate solution was instilled in one eye of these rabbits one hour and again 45 minutes prior to instillation of the cholinergic drug. In all of these rabbits the pupil was widely dilated and no response to light could be demonstrated. Again each anticholinesterase agent was instilled every 10 minutes for two hours. Not a single rabbit showed any significant change in pupil size. It was therefore concluded that atropinization had been complete and also that no true antagonism between atropine and anticholinesterase agents exists.

When atropinization is not complete, there is, no doubt, considerable variation of ability of these miotics to overcome the atropine effect. Since it is difficult actually to determine the degree of atropinization, we must assume they will probably counteract atropine in direct proportion to their ability to cause miosis in the normal eye. In other words, the difference is quantitative rather than qualitative.

HUMAN EXPERIMENTS

For each agent tested, 10 to 12 patients were used. These people, patients on the medical service, suffered from a variety of medical ailments. The pupillary reaction to light and intraocular pressure were recorded prior to the experiment. Those with obvious or questionable ocular defects were not accepted for the study.

Their ages ranged from 17 to 84 years. Each group contained young and old, male

and female patients and was considered to be representative.

Following the measurement of the size of the pupil of each eye and recording of the intraocular pressure (Schiotz) one drop of the agent to be tested was instilled into the conjunctival sac of the right eye; the left eye was used as a control. Both pupils were measured at regular intervals thereafter until the effect of the miotic had worn off and the pupils were again of equal size.

The intraocular pressure was recorded once again one hour after instillation of the miotic. The average pupil size was calculated for each group at each time interval and the average tension was determined for each group. Local ocular irritation and ocular complaints were also noted.

RESULTS

Physostigmine salicylate in a one-percent solution produced a maximal miosis in 20

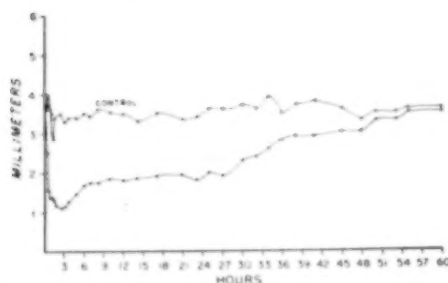


Fig. 1 (Linn and Tomarelli). Physostigmine salicylate (one percent). Ordinate represents pupil size in mm.; abscissa, time in hours.

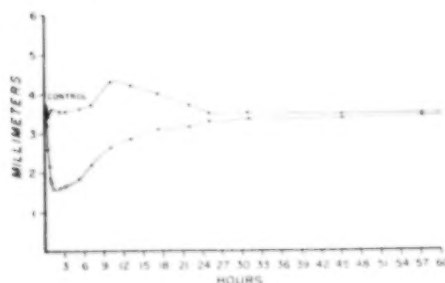


Fig. 2 (Linn and Tomarelli). Stigminene bromide (eight percent).

minutes. Maximal miosis persisted about four hours (fig. 1) although there was a persistent miosis of marked degree for about 27 hours.

There was a gradual relaxation of miosis after 27 hours until at 79 hours the pupils were equal in size in all cases. The rapidity of action and duration of maximal action were similar to those in the rabbit but the duration of action was much longer in the normal human eye.

One hour after instillation of physostigmine, the intraocular pressure had risen an average of 0.5 mm. Hg (Schiotz). Considerable congestion of the conjunctival and ciliary vessels occurred in all patients and persisted for two to three days. Many of the patients complained of blurred vision and some of ocular pain.

Stigminene bromide in an eight-percent solution was less rapid in action, requiring 40 minutes for maximal miosis. This delayed action of stigminene was also seen in rabbits. It is the slowest of all the anticholinesterase agents in producing a response.

Maximal miosis was maintained for six hours (fig. 2) but there was a rapid relaxation of miosis so that after 25 hours only 0.2-mm. difference in size of the pupils remained which persisted 93 hours. Again the miosis produced in rabbit eyes was similar but shorter in duration.

Actually an effective miosis persisted longer with physostigmine than with stigminene, although maximal miosis did not persist as long. Stigminene, on the other hand, in one hour had produced a fall of 3.0 mm. Hg (Schiotz) in the intraocular pressure. A mild conjunctival reaction occurred in most but not all of the eyes.

Neostigmine bromide in a five-percent solution was found to be the least effective of any drug tested in ability to produce miosis. In the first series of eyes studied, the maximal miosis obtained was less than with any other drug and all pupils had returned to normal size after 14 hours.

Although Simonelli⁶ has stated that a solu-

tion of neostigmine (prostigmine) was completely stable, it was suspected that there was a decreased potency of the particular sample used in this study because neostigmine was found to be relatively much more potent in rabbits. The sample used was probably over two years old but had remained sealed until our use.

A second series of human eyes was tested with a fresh supply of neostigmine and a better response was obtained. Maximal miosis of adequate degree was obtained in 30 minutes which persisted for three hours (fig. 3). All perceptible miosis disappeared after 20 hours. Even with the fresh neostigmine, the duration of maximal miosis was shorter than that of rabbits.

The intraocular pressure, on the other hand, fell an average of 4.2 mm. Hg (Schiotz) one hour after instillation of neostigmine in the normal human eye. This was the greatest tension fall of any agent. The local reaction was very mild. Less than half of the patients had any symptom or sign of ocular irritation.

Tetraethyl pyrophosphate (TEP) in a 0.1-percent solution produced a maximal miotic effect in 20 minutes. The duration of maximal miosis cannot be accurately stated because there was a gradual relaxation of the pupil beginning in about 10 hours (fig. 4). The total duration of miosis was 190 hours. This characteristic of gradual relaxation of miosis was observed also in the rabbit studies.

The intraocular pressure one hour after instillation of TEP had fallen an average of 2.4 mm. Hg (Schiotz). The ocular reaction was mild. A congestion of the conjunctival vessels lasted about two days or less.

Di-isopropyl fluorophosphate (DFP) in a 0.1-percent solution produced a maximal miotic effect in 20 minutes. Maximal miosis continued for about 100 hours when a gradual relaxation of miosis began (fig. 5). After a period of 446 hours, the miotic effect had ceased in all but a few patients who showed some miosis several more days.

One hour after the instillation of DFP, the intraocular pressure had fallen an average of 1.3 mm. Hg (Schiotz). A severe local reaction resulted after instillation of DFP. Marked conjunctival and ciliary injection appeared which persisted for five to seven days. The patients complained bitterly of ocular pain as well as frontal and parietal headache. Since the local reaction with DFP was the most severe, we felt that the concentration chosen in this study was stronger than one should use in glaucoma therapy.

COMMENT

A composite picture of the rapidity of action of these drugs is represented in Figure 6. There is very little difference in speed of action of physostigmine, TEP, and DFP. Neostigmine is somewhat slower in action and stigmatine is definitely the slowest.

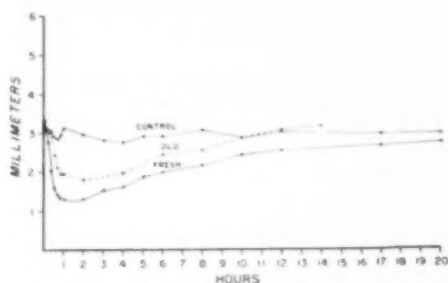


Fig. 3 (Linn and Tomarelli). Neostigmine bromide (five percent). A comparison of old and fresh solutions. The pupil size of the control eye for the fresh neostigmine only is recorded.

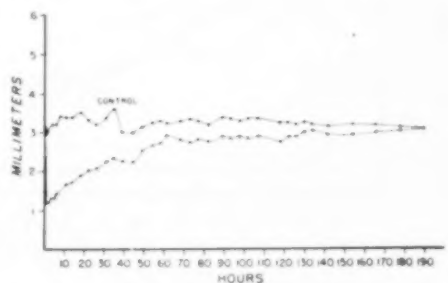


Fig. 4 (Linn and Tomarelli). Tetraethyl pyrophosphate (0.1 percent).

Since all of the anticholinesterase agents we have tested produce their maximal action in 40 minutes or less, this factor should not be considered important in choosing one of them for the treatment of glaucoma.

The great variation among the group is in duration of action. In Figure 7, we have plotted the duration of action of each drug as measured by the difference in the size of the pupil of the treated and control eye. In this way, environment factors affecting both pupils have been eliminated.

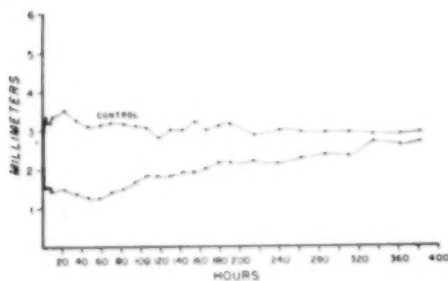


Fig. 5 (Linn and Tomarelli). Di-isopropyl fluorophosphate (0.1 percent).

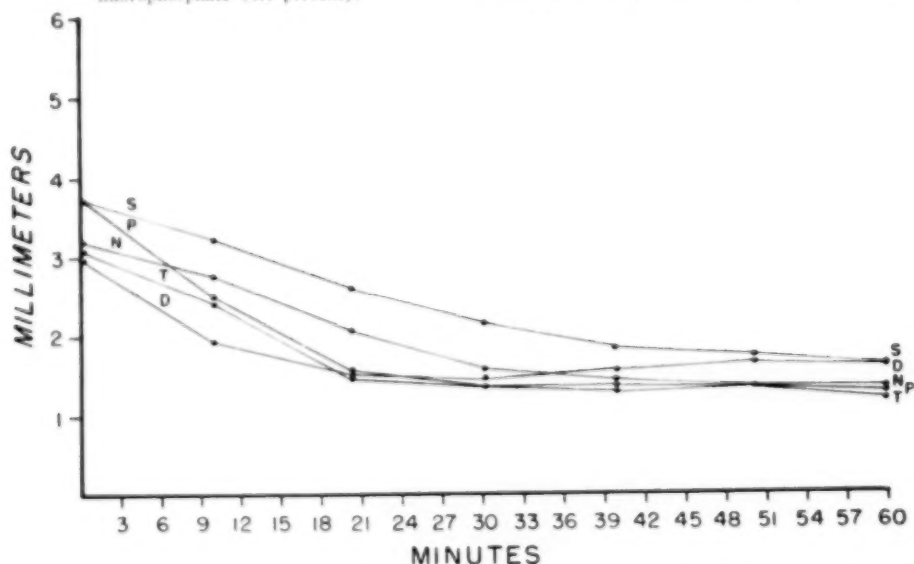


Fig. 6 (Linn and Tomarelli). Rapidity of action of various agents tested. (S) Stigminene bromide (eight percent). (P) Physostigmine salicylate (one percent). (N) Neostigmine bromide (five percent) (T) Tetraethyl pyrophosphate (0.1 percent). (D) Di-isopropyl fluorophosphate (0.1 percent).

The pronounced superiority of DFP in maintaining miosis is quite evident. This difference would probably be less if a weaker and, therefore, less irritating solution had been used. The gradual relaxation of miosis after instillation of TEP is not as evident in this graph.

If one could prove that the effect on the intraocular pressure of a glaucoma patient parallels directly the miotic effect, there would be no point in using neostigmine or stigminene in treatment.

The fall in intraocular pressure after instillation of one drop of each of these miotics in a normal human eye shows a rough correlation with amount of ocular irritation produced (table 1). Physostigmine produced a rise in tension.

DFP produced the least fall in tension of any of the other drugs, and has been reported by von Sallmann and Dillon⁷ to have produced a rise in tension. This has been explained as being the result of the dilatation of the capillaries of the iris and ciliary body. Possibly a congestion of the aqueous veins

is also an explanation and the effect of each of these drugs upon the aqueous veins should be studied.

Clinical experience in the treatment of glaucoma with these drugs does not give any evidence of an effect on the intraocular pressure similar to that recorded in these normal eyes. Therefore, no conclusions can be made from these tension findings as to the relative value of the anticholinesterase agents in the treatment of glaucoma.

In noting the pupil size of the control eye after instillation of a miotic in the opposite eye, one can observe a temporary or prolonged dilatation of that pupil to a mild degree. Only neostigmine fails to show this contralateral pupillary dilatation. This finding is not the result of environmental influences.

Boriani⁸ in a careful and thorough series of experiments has demonstrated a retinopupillary reflex. The pupillary dilator center is stimulated by the decreased light strik-

ing the retina of the miotic eye. Since the stimulus to dilate the pupils is transmitted from the dilator center to both eyes equally, a dilatation of the opposite pupil results. If the optic nerve of the eye receiving the miotic is severed, this reflex is abolished.

Apparently the miosis produced by neostigmine was not sufficient to activate this reflex. We feel this reflex accounts for the rise in tension frequently seen in an eye which previously had been normal, when strenuous miotic therapy is being administered to the opposite eye.

If miosis is any criterion of the effectiveness of an anticholinesterase agent in the treatment of glaucoma, physostigmine, TEP, and DFP are the most potent of these drugs available today.

We cannot support the pessimism expressed by Grant in his recent report.⁹ Although he found a drug sensitivity to develop in a number of his cases, we do not feel this is a valid objection. We have noted

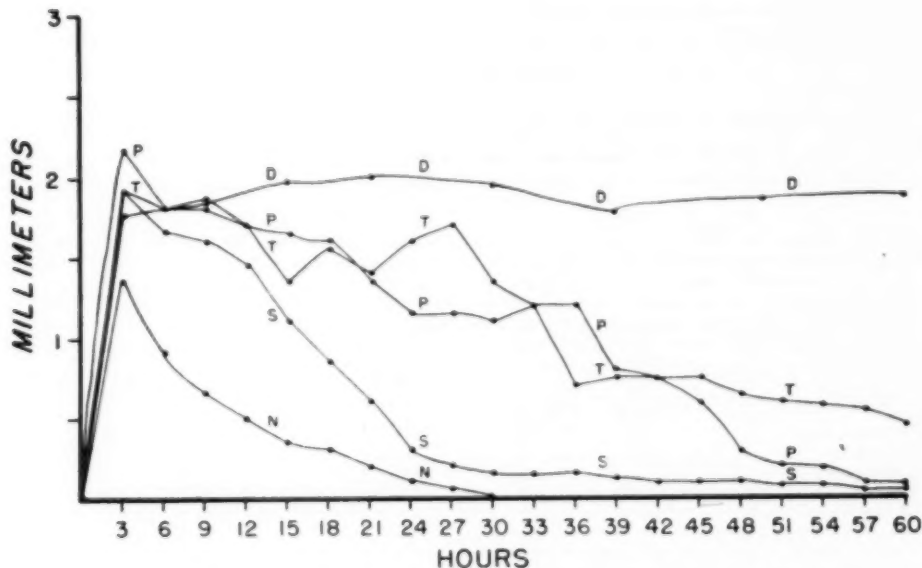


Fig. 7 (Linn and Tomarelli). Duration of action as measured by a difference in pupil size of the treated and control eyes. (S) Stigminene bromide (eight percent). (P) Physostigmine salicylate (one percent). (N) Neostigmine bromide (five percent). (T) Tetraethyl pyrophosphate (0.1 percent). (D) Di-isopropyl fluorophosphate (0.1 percent).

TABLE 1
EFFECT OF ANTICHOLINESTERASE AGENTS ON OCULAR TENSION

	Tension* before Instillation	Tension One Hour after Instillation	Rise or Fall	Conjunctival and Ciliary Irritation
Physostigmine	22.7	23.2	+0.5	+++
Stigminene	20.3	17.3	-3.0	++
Neostigmine	19.6	15.4	-4.2	+
TEP	20.7	18.3	-2.4	++
DFP	18.4	17.1	-1.3	++++

* Each tension is the average of 10 to 12 patients.

a drug sensitivity in many of our patients using physostigmine and in others using atropine. We have no intention of discontinuing the use of these drugs. The mild local reaction and the prolonged duration of action of TEP makes it ideal for the treatment of glaucoma. We feel further investigation is indicated before TEP is dropped from the list of drugs useful in glaucoma.

SUMMARY AND CONCLUSIONS

1. An evaluation of five anticholinesterase agents has been made on normal rabbit and human eyes. The concentration of each drug tested corresponds to the strongest concentration which might be used in the treatment of glaucoma.

2. Physostigmine, di-isopropyl fluorophosphate, and tetraethyl pyrophosphate were most rapid in action.

3. Di-isopropyl fluorophosphate, tetraethyl pyrophosphate, and physostigmine caused the most prolonged miosis in the order named.

4. Neostigmine, stigminene, and tetraethyl pyrophosphate caused the least local ocular irritation and the greatest fall of intraocular pressure of the normal eye. Physostigmine caused a rise of the intraocular pressure.

5. In our rabbit experiments, we failed to demonstrate any antagonistic effect of any drug in this group to atropine when atropinization was complete. In a partially atropinized pupil, no significant difference in ability to overcome atropine was observed.

6. A dilatation of the pupil of the control eye of mild degree occurred in most instances. We have suggested this as an explanation of the occasional occurrence of an acute tension rise observed in a previously normal eye during the course of intensive miotic therapy of the fellow eye.

7. In spite of a previous unfavorable report on tetraethyl pyrophosphate, we feel further clinical trial is indicated because of desirable characteristics of that drug observed in this study.

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TABLE 2
EFFECT OF ANTICHOLINESTERASE AGENTS
UPON NORMAL PUPILS

	Rapidity of Action	Duration of Maxi- mal Miosis	Total Duration
	(min.)	(hours)	(hours)
Physostigmine	20	4-27	79
Stigminene	40	6	93
Neostigmine	30	3	29
TEP	20	10-30	190
DFP	20	100	454

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DISCUSSION

DR. W. MORTON GRANT [Boston]: Studies of cholinesterase inhibitors are primarily interesting in ophthalmology for the usefulness or potential usefulness of these drugs in the treatment of glaucoma. This sort of study is necessary for proper selection from among the considerable number of cholinesterase inhibitors that are known because the cholinesterase inhibitors have a common mode of action. Their common denominator is that they all act through acetylcholine. Therefore, we would expect that they would all fundamentally have the same actions in the eye, that is, just the actions of acetylcholine. Differences among cholinesterase inhibitors would be only in their side properties, that is, in their duration of action, in their contact toxicity, or in their stability.

Duration of action which has been principally studied here is interesting and important to us in the practical use of the drug because of the frequency with which it need be administered. The short-acting drug can be effective in an eye only by frequent administration, but a long-acting drug like DFP may have the advantage, on the one hand, of being used only say, once a day, but have the disadvantage, on the other hand, that a cumulative effect is easily obtained, the succeeding doses adding upon the effect of the first doses given, so that there is an increasing effect over several days. Dosage is started today and in three days the dose in effect in the eye may be built up to a greater level than the original. So, that is a consideration that must be taken into account in connection with duration.

In connection with toxicity, we have the local irritative effect which probably has nothing to do with the acetylcholine but is due to the physical-chemical properties of the drug itself. Also, the property of producing sensitization is one that cannot be neglected readily.

In the case of TEP, I felt that the incidence of sensitization was high enough to make this drug less desirable than some others. In other words, to make it worth while to keep on looking for some other drug that could be tolerated by a larger proportion of the patients. It is a matter of opinion as

to what is a tolerable percentage of sensitization.

On the question of stability, we might consider that, of the drugs that have been tested so far, there are two groups: the organic phosphate esters, such as TEP and DFP, and the nitrogen bases, the alkaloids, such as eserine and prostigmine.

The principal difference in those so far tested is that organic phosphates are poorly stable in water; they decompose in a matter of hours to inactive products. Therefore, they have had to be used in oil, and if somebody got some tears or water in the oily solution, there might be decomposition of the drug and, before the patient was aware of it, his condition would be out of control.

The alkaloids are water-soluble and water-stable for considerable periods and that is an advantage in their favor.

There is another drug that has been investigated in Europe and is among the organic phosphates, a di-ethyl paranitrophenyl phosphate. This substance, unlike the other organic phosphates, is water-soluble and water-stable and, according to the reports in Europe, is effective in the treatment of glaucoma. A study such as Dr. Linn's will be necessary for comparison with our standard drugs to see whether this one offers any advantages.

Incidentally, a lot of these cholinesterase inhibitors are toxic to insects and the literature on insecticidal agents is a good source for information on new compounds of miotic potentialities. TEP was first investigated in Germany for its insecticidal properties. Parathion and mintacol, diethyl paranitrophenyl phosphate, were also first studied as insecticides.

DR. JAY G. LINN, JR. (closing): I wish to thank Dr. Grant for his discussion, I might add something that is in the paper but that I forgot to mention. The irritation from DFP was so marked in these patients that we did not think a 0.1-percent solution in peanut oil was advisable in routine treatment of glaucoma. I think many of you have also had experience with patients who could not tolerate the 0.1-percent solution.

ELECTROENCEPHALOGRAPHIC CHANGES IN STRABISMUS*

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Chicago, Illinois

The present clinical study was initiated after the observation that many children, in whom the electroencephalogram showed occipital lead abnormalities, had associated ocular problems. To clarify the nature of this relationship, a detailed study was made of 1,345 children under the age of 16 years.

A preliminary report by Levinson, Gibbs, Stillerman, and Perlstein¹ dealt with the findings in 1,245 patients. It was limited to the relationship between the electroencephalographic occurrence of occipital foci and neuro-ocular pathology in general.

The present report attempts a more detailed evaluation of this relationship relative to types of strabismus, amblyopia ex anopsia, retinal correspondence, and fusion status.

DISTRIBUTION OF CASES

The 1,345 cases in this study were divided into three groups. The age range was from two to 16 years. The first group contained 640 patients for whom complete history and neurologic and eye examinations were available. Of this group, 180 normal children without neurologic or an ocular pathologic condition comprised the control series. The remainder of this group was made up of 460 consecutive cases of cerebral palsy seen in a pediatric neurology office and clinic practice.

The second group consisted of 605 children with seizures and abnormal electroencephalograms for whom a record of the eye findings was available, but for whom complete history and physical findings were not given.

The third major group consisted of 100 cases selected from the eye clinics of the Illi-

nois Eye and Ear Infirmary and the Research and Educational Hospitals of the University of Illinois. An attempt was made to choose patients who were normal, except for the ocular pathologic condition. Any child whose history or physical examination was suggestive of central nervous-system involvement was screened out of the third group.

NATURE OF THE EYE DISORDERS

The first two groups comprised 1,245 cases of which 361 had eye disorders. Strabismus was the most common condition, and accounted for 73 percent of the total cases in which an ocular pathologic condition was present. Central blindness was noted in approximately 16 percent. The remaining 11 percent consisted of cases of congenital cataracts, paralysis of vertical gaze, and nystagmus. Visual aura were not included as eye findings in this study, although high correlation with occipital foci was noted (table 1).

In the third group, 89 of 100 cases were strabismus problems. The remaining 11 cases in this group consisted of congenital cataracts, ptosis, nystagmus of ocular origin associated with compound myopic astigmatism, retrolental fibroplasia, posttraumatic amaurosis, and optic atrophy. An analysis of the eye disorders in Group 3 is shown in Table 2.

THE ELECTROENCEPHALOGRAM

In 1929, Berger discovered that changes in electrical potential could be recorded by the application of electrodes to the human scalp. The oscillations in electrical potential occur rhythmically at a frequency of six to 30 per second in the adult, but are frequently as slow as four to six per second in infants. The amplitude varies normally from five to 100 microvolts. The waves recorded from the scalp are cortical in origin, but are modified by the activity of deeper centers and by sensory stimulation.

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Visual stimulation is particularly effective in modifying the electroencephalogram. Pathologic changes in the electroencephalogram reflect alteration of function of a portion of the cortex or connected deeper centers. Such changes are common in epilepsy, brain tumors, abscesses, and, in fact, in all conditions producing brain damage, irritation, or disorders of neuronal metabolism.

Nonfunctioning or destroyed areas of cortex are not readily detected in the electroencephalogram because the activity of surviving brain cells masks the cells which have been destroyed.

All electroencephalograms in this study were taken with the patient both awake and asleep. Sleep was either spontaneous or induced with 0.75 to 1.5 gr. of seconal. Sleep records were considered necessary for the proper study of this series, since during sleep a much higher proportion of abnormalities becomes manifest in the electroencephalogram.²

Reference electrodes and the Grass eight-channel electroencephalograph instrument were used in all cases. From eight to 12 leads were employed and, in many cases, both a low and a high occipital lead were used. The leads were glued to the scalp with collodion as shown in Figure 1. The procedure is entirely painless and nonhazardous.

We considered spike foci and slow-wave foci to be major pathologic alterations.^{3,4} Persistent amplitude asymmetry between the right and left occipital leads, and limited to this area, was classified as a minor electroencephalographic abnormality. Present experience marks this asymmetry as abnormal, since it did not occur in our normal control group.

The normal electroencephalographic pattern is shown in Figure 2. The presence of spike foci may be seen in the right occipital lead in Figure 3. Slow-wave foci are represented in the right occipital lead in Figure 4. Persistent amplitude asymmetry is pictured in Figure 5. The left occipital lead with low voltage is considered pathologic, since this

TABLE 1
DISTRIBUTION OF EYE DISORDERS IN COMBINED GROUPS 1 AND 2
(1,245 cases)

No eye disorders	884
Eye disorders present of which	361
Strabismus occurred in	73%
Central blindness occurred in	16%
Congenital cataracts	
Paralysis of vertical gaze	11%
Nystagmus	

relationship is maintained throughout the tracing.

All borderline or equivocal tracings were considered to be normal, and only those with patent irregularities were classified as abnormal. For purposes of this study, electroencephalographic abnormalities were divided into the *generalized* group, in which the seizure activity occurred simultaneously in all leads, and the *focal* group, in which the electroencephalographic disturbance occurred independently in one or more areas.⁵ The focal group included those in which the occipital area was involved alone or in combination with other areas.

TABLE 2
NATURE OF EYE DISORDERS IN GROUP 3
(100 cases)

I. Strabismus cases	89
Esotropia	65
Monocular	36
Right	18
Left	18
Alternating	29
Exotropia	22
Monocular	4
Right	3
Left	1
Alternating	18
Hypertropia	2
II. Other ocular pathologic findings	11
Congenital cataract	3
Posttraumatic amaurosis	1
Optic atrophy (etiology undetermined)	1
Retrolental fibroplasia	1
Ocular nystagmus and compound myopic astigmatism	3
Blepharoptosis	2



Fig. 1 (Stillerman, Gibbs, and Perlstein). From eight to 12 leads were glued to the scalp with collodion.

RESULTS

In 180 control children, namely those with no history of seizures and completely normal physical examination, only 0.5 percent had occipital foci (table 3).

The group of 460 cerebral-palsy cases includes some patients with pyramidal and some with extrapyramidal tract involvement. Seizures and abnormal eye findings were present in some and absent in others.

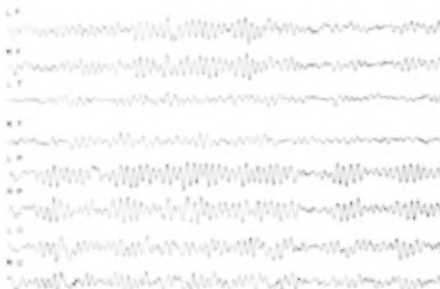


Fig. 2 (Stillerman, Gibbs, and Perlstein). The normal electroencephalographic pattern.

A high incidence of focal electroencephalographic abnormalities was present. Of the 305 cases with normal eyes 38 percent had occipital foci, and 35 percent had changes in other leads. Focal involvement was twice as great in the occipital area (74 percent) and only one fourth as great in extraoccipital areas (nine percent) in the group with pathologic findings in the eye, as compared to the group with normal eyes (table 3).

No significant statistical correlation was demonstrated between electroencephalographic abnormalities and sex, age, or race, so these subclassifications were omitted from the table for purposes of clarity.

To determine whether a correlation existed between the type of eye involvement and occipital foci, the 155 cerebral-palsy cases with neuro-ocular pathologic findings were analyzed with reference to the type of eye disorder. Strabismus occurred in 105 of the 155 cases, and 80 (76 percent) had associated occipital foci. Similarly, 22 of the 24 cases with central blindness (92 percent) had occipital foci. Of the remaining 26 cases, which included those with congenital cataract, paralysis of vertical gaze, and nystagmus, 50 percent had occipital foci (table 4).

The presence of seizures in cerebral palsy increases the incidence of focal seizure activity throughout the brain,⁶ including the occipital areas (table 5). Even when the eye

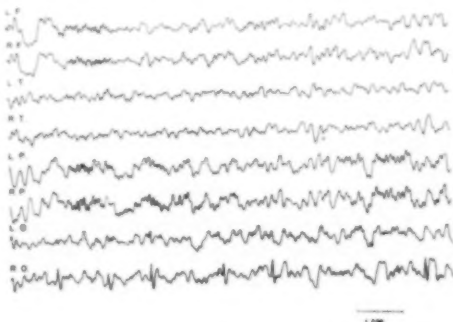


Fig. 3 (Stillerman, Gibbs, and Perlstein). The presence of spike foci may be seen in the right occipital lead.

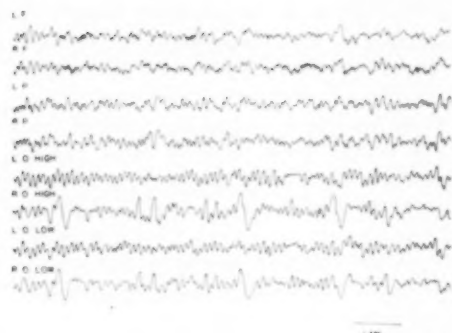


Fig. 4 (Stillerman, Gibbs, and Perlstein). Slow-wave foci are represented in the right occipital lead.

findings were normal, the incidence of focal occipital electroencephalographic abnormalities was doubled (52 percent to 25 percent) when seizures co-existed. However, when, in addition to seizures, eye disorders were present, a significantly greater percentage of occipital focal electroencephalographic changes occurred than when the eyes were normal (82 percent to 52 percent). There was a concomitant drop in focal activity in the other leads when eye disorders were present.

The second group of patients with which this report deals consisted of 605 patients with seizures whose electroencephalograms demonstrated focal abnormalities. Of this group 206 had eye disorders.

The correlation of electroencephalogram

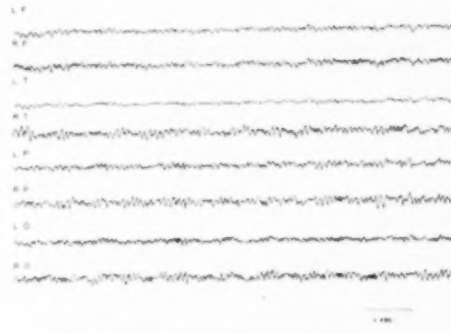


Fig. 5 (Stillerman, Gibbs, and Perlstein). Persistent amplitude asymmetry.

findings with the presence of eye disorders is noted in Table 6. Of 253 patients with abnormal electroencephalographic foci sparing the occipital region, only nine percent had pathologic eye findings. Of 352 patients with occipital foci, 52 percent had abnormal neuro-ocular findings.

A consideration of foci limited to a specific area of the brain reveals that occipital involvement is associated with clinical eye deviations in a significantly higher percentage of cases (63 percent) than when isolated involvement of frontal (three percent), temporal (six percent) and parietal (eight percent) areas occurs.

Strabismus comprised approximately 75 percent of the eye cases in this group, central blindness about 20 percent, and nystag-

TABLE 3
ELECTROENCEPHALOGRAPHIC AND EYE DISORDERS IN NORMAL AND CEREBRAL PALSIED CHILDREN

Clinical Classification		Total Cases	EEG Classification in Percent				
			Normal	General Seizure Activity	Focal Abnormality		Total
					Occipital	Other	
Normal		180	98	0	0.5	1.5	100
Cerebral Palsy 460 Cases	Eyes normal	305	26	1	38	35	100
	With strabismus or other eye disorders	155	17	0	74	9	100
	Total	640					

TABLE 4
INCIDENCE OF OCCIPITAL SPIKING IN ELECTROENCEPHALOGRAPHIC IN 155 CEREBRAL PALSY CASES WITH EYE DISORDERS OF VARIOUS TYPES

	Total Cases	Occipital Spiking	
		Number	%
Strabismus	105	80	76
Central blindness	24	22	92
Congenital cataracts Paralysis of vertical gaze Nystagmus	26	13	50

mus, congenital cataracts, or a combination of these conditions, the remainder. In this group, just as in the first group studied, cortical blindness and strabismus were the ocular deviations most frequently associated with abnormal occipital foci.

The third group of cases comprising this study consisted of 100 patients whose sole problem was ocular (table 2). Of these, 82 had normal and 18 had abnormal electroencephalogram tracings (table 7). Of the 18 abnormal electroencephalographic tracings, all changes were limited to the occipital leads. Nine cases had persistent amplitude asymmetry, eight had spike foci, and one had slow-wave foci. All of the abnormal patterns were found among the 89 strabismus patients, the 11 with miscellaneous ocular pathologic findings having normal tracings.

An analysis of the abnormal electroencephalograms with reference to the types of strabismus revealed that five of the eight occipital spikes occurred in children with alternating exotropia, despite the fact that there were almost three times as many patients with esotropia as exotropia. On the other hand, the nine patients with persistent amplitude asymmetry included seven with esotropia and two with exotropia. The two hypertropias, with definite parietic components, had normal electroencephalograms.

Our findings, though based on a relatively small series, would indicate the occipital abnormalities in the electroencephalogram occur about twice as frequently in exotropia as in esotropia (32 percent to 17 percent), and that when the occipital abnormality consists of spikes, the incidence in exotropia is about four times that of esotropia (22 percent to 5 percent).

AMBLYOPIA EX ANOPSIA

An attempt was made to correlate the presence of amblyopia ex anopsia with a pathologic electroencephalographic pattern. A diagnosis of amblyopia was made only if subjective verification was possible. Questionable cases were eliminated.

A total of 21 amblyopes were found in the entire strabismus series, 15 of these having entirely normal electroencephalograms. As can be seen from Table 8, occipital electro-

TABLE 5
RELATION OF ELECTROENCEPHALOGRAPHIC TO EYE AND CONVULSIVE DISORDERS
(460 cerebral palsy cases)

Clinical Classification		Total Cases	EEG Classification in Percent			
			Normal	General Seizure Activity	Focal Seizures	
Eyes normal	No seizures	172	37	1	25	37
	With seizures	133	13	2	52	33
With eye disorders	No seizures	105	21	0	71	8
	With seizures	50	6	0	82	12

TABLE 6
LOCALIZATION OF ELECTROENCEPHALOGRAPHIC FOCI AND EYE DISORDERS
(605 cases with seizures)

Location of Focus	Total Cases	With Eye Disorders	
		Number	%
Occipital spared—Total	253	22	9
Frontal alone	34	1	3
Temporal alone	98	6	6
Parietal alone	51	4	8
Combined	70	11	16
Occipital involved—Total	352	184	52
Alone	136	86	63
Combined with other areas	216	98	45

encephalographic abnormalities were found in 29 percent of strabismus cases with amblyopias, as compared to 18 percent of strabismus without amblyopia.

This apparent increase in the incidence of electroencephalographic abnormality in the presence of amblyopia is perhaps fortuitous, but it may be real, since amblyopia is more commonly found in esotropia, where electroencephalographic abnormalities are less frequent than in exotropia.

RETINAL CORRESPONDENCE

Reliable determination of retinal correspondence was obtained in 52 cases, employing the synoptophore and the after-image test. Normal retinal correspondence was elicited in 34 cases, and anomalous correspond-

ence in 18. Only one case in the latter group demonstrated harmonious anomalous correspondence, nine had unharmonious correspondence, and eight had no particular area in the deviating eye that corresponded directly with the fixating macula. This situation parallels the "state without functional correspondence" described by Adler and Jackson.⁷

The remaining 37 strabismus cases were eliminated from consideration because 20 provided insufficient cooperation with which to determine the correspondence status, and 17 gave conflicting results on testing with the haploscope and the after-image devices.

Of the 18 patients with abnormal electroencephalograms, only one had associated anomalous retinal correspondence. Nine of

TABLE 7
ELECTROENCEPHALOGRAPHIC FINDINGS IN NORMAL PATIENTS WITH EYE DISORDERS
(100 cases)

Clinical	No. Cases	Normal	Occipital EEG Changes			Total
			Spikes	Asymmetry	Slow-Wave	Abnormal
Strabismus Total	89	71	8	9	1	18 (20.2%)
Esotropia	65	54	3 (5%)	7 (11%)	1	11 (17%)
Exotropia	22	15	5 (22%)	2 (9%)	1	7 (32%)
Hypertropia	2	2	0	0	0	0
Miscellaneous Eye pathologic findings	11	11	0	0	0	0
Total	100	82	8	9	1	

TABLE 8
ELECTROENCEPHALOGRAM AND AMBLYOPIA
IN STRABISMUS

		No. Cases	EEG Findings	
			Normal	Abnormal
Strabismus		89	71	18
No amblyopia		68	56	12 (18%)
Amblyopia		21	15	6 (29%)

the remaining 17 cases with pathologic irregularities in the electroencephalographic tracings had normal retinal correspondence, while eight cases fell in the group with undetermined or equivocal correspondence. The additional 25 strabismus cases with normal retinal correspondence had normal electroencephalograms.

It is believed, therefore, that no correlation had been demonstrated between anomalous retinal correspondence and pathologic bioelectrical activity as recorded in the electroencephalogram.

FUSION

The presence or absence of suppression and the fusion status were determined by means of Worth's four-dot test, the major amblyoscope, and the Three Dimensional Company's polaroid "fly." Reliable estimation of fusion was obtained in 52 of 89 cases.

The breakdown, correlating fusion status with electroencephalographic findings, employs the classical terminology (table 9). On the basis of our data no correlation can be established between fusion difficulties and the presence of occipital abnormalities in the electroencephalogram.

LATERALITY

A study was made to see if there was a relationship between the side of the ocular deviation and the side of the electroencephalographic abnormality. No correlation on the basis of laterality was observed.

DISCUSSION

A significant number of children with stra-

bismus and central blindness have associated occipital lead abnormalities in the electroencephalogram. This relationship exists in the strabismus group whether or not organic brain disease or seizures are present.

There are, as yet, too few data to establish a definite relationship between the types of strabismus and occipital lead abnormalities in the electroencephalogram. However, the trend evidenced in our material, with 32 percent of exotropes having associated occipital lead abnormalities, makes it imperative that a larger number of exotropia cases be studied to ascertain whether a true statistical difference exists between the esotropias and the exotropias.

We have found no basis in fact to support the contention of Dyer and Bierman⁸ that a high percentage of children with amblyopia ex anopsia in strabismus have generalized electroencephalographic abnormalities. Furthermore, we have not been able to establish an unequivocal correlation between amblyopia ex anopsia and the occipital lead changes which comprised the predominant electroencephalographic feature in cases with ocular pathologic findings.

The electroencephalographic record in children contains a large number of normal variations. The interpretation of such tracings should be rendered with greater caution and restraint than is necessary in the adult records, where the abnormal changes are more clearly defined.

Failure to correlate amblyopia ex anopsia, fusion, and retinal correspondence with abnormal electroencephalographic findings makes it questionable whether the electroencephalogram will be of any aid in solving the riddle of the sensorial aspects of the strabismus problem. However, it may be a useful tool in evaluating the individual squint problem. In two of our intermittent exotropias there is a strong suspicion that the episodes of ocular deviation may coincide with the bursts of abnormal electrical discharge in the occipital areas.

The presence of abnormal electrical ac-

TABLE 9
FUSION STATUS AND ELECTROENCEPHALOGRAM
(89 strabismus cases)

71 Cases with Normal EEG

	No. Cases	EEG Findings			
		Normal	Spike	Asymmetry	Slow-Wave
Fusion status determined	41	41			
No fusion	12				
Simultaneous					
Macular perception	14				
Fusion with amplitude	11				
Stereopsis	4				

18 Cases with Abnormal EEG

Fusion status determined	11	0	4	6	1
No fusion	4		1	3	
Simultaneous					
Macular perception	4		3	1	
Fusion with amplitude	1				1
Stereopsis	2			2	

tivity in the brain of a child with strabismus does not establish a causal relationship, but must make one suspicious that abnormal supranuclear influences are at play.

We are investigating the relationship between such electroencephalographic changes and intermittent tropias by recording simultaneous electroencephalograms and electrical eye potentials. Eye potential differences are being studied according to the technique described by Callahan and Redlich.⁹

The first 36 cases sent from the Motility Clinic for electroencephalographic study were chosen at random. Of these, 30 percent had abnormal electroencephalograms. Careful questioning of these patients, whose problems were thought to be solely ocular, revealed clues suggesting central nervous-system involvement. These cases were discarded from our series, but they point up the fact that a high number of squints with a neurologic basis may be overlooked unless a careful investigation is instituted.

SUMMARY

1. A clinical correlation between electroencephalographic studies and strabismus, as well as a group of miscellaneous eye disor-

ders, has been made in 1,345 children under the age of 16 years.

2. In children with organic brain disease causing cerebral palsy, electroencephalographic foci in the occipital region occurred almost twice as frequently in the presence of abnormal eye findings. The nature of this relationship prevailed whether or not seizures were present.

3. In 605 cerebral palsy cases with seizures and ocular pathologic findings, predominantly strabismus, electroencephalographic foci involving the occipital region were six times more common than all other foci combined.

4. Of 89 normal children with strabismus, 20.2 percent had occipital lead abnormalities in their electroencephalograms. In the control group of 180 normal children without strabismus or other ocular pathology only 0.5 percent had occipital lead abnormalities in their electroencephalograms.

5. Occipital abnormalities in the electroencephalogram occurred twice as frequently in the normal children with exotropia as in esotropia (32 percent to 17 percent). When the occipital abnormality consisted of spikes, the incidence in normal children with exotropia was approximately four times that

with esotropia (22 percent to five percent).

6. No abnormal electroencephalograms were found in the group of normal children with miscellaneous ocular pathologic conditions. It is probable that an ocular pathologic process limited to the peripheral organ does not affect electroencephalographic patterns.

7. No correlation was demonstrated be-

tween abnormal electroencephalographic findings and fusion, the laterality of the deviation in strabismus, and retinal correspondence. The equivocal relationship between electroencephalographic disturbances and amblyopia ex anopsia is discussed.

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DISCUSSION

Dr. GEORGE GUNDBER (Chicago): The authors have, in this paper, placed the eye in the position where it belongs, within the central nervous system. We as ophthalmologists fail many times to recognize this fact. It is a fact that strabismus, from a neurologic viewpoint, divides itself into three main types: (1) That associated with defects of the central nervous system such as the authors have discussed, where there are lesions in the cortex; (2) that type associated with derangements of the central nervous system, such as accommodative esotropia in which there are no lesions; and (3) that type associated with lesions of the peripheral-nervous system.

Encephalographic examination is one of the methods whereby we can ascertain when strabismus results from defects in the central nervous system. It is interesting, however, to realize that here we have a method of diagnosis which is not foolproof. This method must be interpreted with certain reservations which are available to most of us.

Another point that I wish to stress is the fact that other evidences exist that the central nervous system is involved in producing strabismus. In a large number of patients with cerebral palsy, we

find the existence of strabismus or some other eye defect, such as conjugate deviations. This interesting observation gives us insight into the fact that strabismus is present in 60 to 70 percent of the patients who have cerebral palsy (I am talking about children predominantly), in whom there exists cortical lesions. It is, therefore, very important to analyze this situation as Dr. Stillerman has done.

An important finding, made here, is that the occipital lobe shows these dominant defects in the electroencephalogram rather than the frontal cortex. We do not know how to explain this observation because we find the frontal cortex which seems to be affected clinically in cases of cerebral palsy associated with strabismus.

The results discussed in this paper are indeed an addition to our knowledge concerning the etiology of strabismus.

Dr. DONALD LYLE (Cincinnati): About a year ago we were setting up our encephalographic apparatus to do some work on nystagmus; we thought we could determine the difference between vestibular nystagmus, the nystagmus due to fatigue, and so on, and our neurologist told me of the splendid

work they were undertaking in Chicago so I wrote to these investigators and they sent me their manuscript. Immediately we thought we might turn our encephalographic study over to this other field. So, we have a modest number of cases that we have examined—22, all together. But we have some ideas and we thought that we might continue this study and try to develop and improve or disprove them.

We tried to examine cases of strabismus of the alternating type, of the monocular type, with and without amblyopia, and of the paralytic type, either supra- or infranuclear. We took the readings with the patients' eyes closed, with their vision suppressed, with their eyes open and reading at 20 feet, with their eyes moving from side to side in a horizontal direction from one corner of the room to the other, and also reading at close range, hoping that we might develop something.

We found in our modest series that, as the essayists said, most of our defects, if they were present at all, were occipital-lobe defects. We found one or two in the frontal or parietal lobe. We were hoping that we might be able to determine why we should find so many in the occipital lobe, whether it is the reflex occiput mesencephalic tract which is chiefly involved in this condition or whether it is the voluntary corticobulbar tract. I thought perhaps the essayists could tell us why it occurs so much more frequently in the occipital lobe than it does in the motor field of the frontal lobe.

We were hoping that possibly we could determine why some of our strabismus surgery is good and some not so good. We thought, possibly, if there was cerebral involvement, we had a poorer chance of getting good results than if it was infranuclear or nuclear, because of the more complex condition present, the more unstable condition present. So I should like to ask the essayist whether he thinks that the reason for this occipital preponderance of spikes, of the abnormalities of the occipital field, is significant of the fact that we are dealing with more of a reflex condition there rather than a voluntary one.

DR. ARTHUR LINKSZ (New York): I am interested in this paper because it reminded me of another paper we heard, I think, in this society, some years ago, by Professor Wald and Dr. Burian. They studied retinal function in cases of amblyopia and found that, as far as pure retinal functions are concerned (such as intensity discrimination or dark-adaptation), there was no difference between cases of amblyopia and other normal cases. This, to my mind, proved clearly that the whole problem of amblyopia and, of course, the whole problem of strabismus, has to be shifted from the eye, from the retina, and from the musculature of the eye to the brain; that the actual problem in strabismus is in the brain.

In that connection, it is significant to see the many cases of generalized pathologic conditions of the brain in the presented material—the cases of palsy which, on the one hand, show changes in the electroencephalogram and, on the other hand, present oculomotor pathologic findings.

There is just one question I would like to ask: The author had two cases of hypertropia in connection with which he made the remark that these cases had no involvement of the electroencephalogram because they were paralytic cases. Do I understand well that he expects in general that cases of purely oculomotor palsy have no involvement of the electroencephalogram? Is there any correlation between the two?

DR. HAROLD FALLS (Ann Arbor, Michigan): I wish to intrude a minute to make a suggestion to the authors that they consider extending their studies to include both unaffected and affected siblings as well as parents. Such family studies will present the investigators with the same gene (and same phenotype). They will not be dealing with a hodgepodge of etiology but will be thus studying the same basic pathologic process in a group of individuals which vary only slightly in environment and modifying genes. Such family studies provide their own controls; that is, the unaffected relatives.

DR. M. L. STILLERMAN (closing): I do not think I can shed any light on Dr. Lyle's question about why we find predominant changes in the occipital leads rather than in the frontal leads. I think his suggestion that these alterations may be of a reflex nature rather than a voluntary one is a good one. However, we must not forget that, despite the fact that we are recording cortical activity from a particular area of the brain, the potential changes are subject to influences from the deeper centers. Certainly the large, unexplored associational pathways, which may be concerned with such things as fusion and other sensory components, may be influencing our records.

As far as Dr. Linksz's question about the difference between the concomitant and the paralytic squints is concerned, I hope I did not mislead you. I did not mean to imply that because there was a paralytic element in the hypertropia, that the electroencephalogram would be normal, although I feel that in pure peripheral nerve involvement without cerebral damage, we would be less likely to have disturbances in the electroencephalogram.

The question is asked whether there has been any attempt to correlate electroencephalographic findings with those found in the electroretinogram. I cannot give you any specific data except to say I know Dr. Burian has been working on that problem in Boston. I have had no correspondence or discussions with him since he started the problem but I do know he is working on it.

STUDIES ON THE PATHOGENESIS OF RETROLENTAL FIBROPLASIA*

FRANKLYN P. BOUSQUET, JR., M.D., AND WILLIAM E. LAUPUS, M.D.
New York

For the past year the Departments of Pediatrics and Ophthalmology at the New York Hospital-Cornell University Medical Center have cooperated in a study to evaluate the role of vitamin E in retrolental fibroplasia. While that study is not complete, frequent serial ophthalmoscopic examinations according to the methods of Owens and Owens† in normal infants and infants developing the disease have established the characteristics of the normal premature fundus and a constant pattern of changes typical of retrolental fibroplasia. These changes in their order of development, plus a tendency to regress, seem to constitute the pathogenesis of the disease.

METHODS

All infants weighing less than 1,650 gm. on admission to the premature nursery of the New York Hospital-Cornell University Medical Center were given routine serial ophthalmoscopic examinations. The initial examination was usually made prior to the removal of the infant from the incubator, and subsequent examinations were carried out at weekly intervals during hospitalization. After discharge, periodic examinations were made in a special follow-up clinic. In infants over the age of six months, when indicated, examinations under anesthesia were performed.

Full mydriasis was effected with one-percent homatropine hydrobromide solution in combination with 2.5-percent buffered oph-

thalmic phenylephrine hydrochloride solution (neosynephrine).

Excellent cooperation was obtained from the infants by means of a standard rubber nipple stuffed with cotton saturated with five-percent dextrose solution.

On admission to the premature nursery, all infants were routinely placed in an incubator, usually of the Gordon-Armstrong or Isolette types. Use of the incubator with constant temperature and humidity regulation and high oxygen concentration was maintained until the infants weighed 1,500 gm. or demonstrated no further need for its continuance.

After an initial fasting period of 12 to 24 hours, the infants were given small feedings of five-percent dextrose solution at intervals of three hours for the next 12 hours. Thereafter, all infants received a formula consisting of diluted, powdered, partially skimmed cow's milk reinforced with dextrin-maltose. Shortly before discharge, a standard dilution of evaporated milk with added dextrin-maltose was substituted for the above formula.

All infants were routinely given four mg. of vitamin K (menadione) intramuscularly on admission. Oral ascorbic acid, 50 mg. daily, was usually begun on the seventh or eighth day of life. Alternate infants received a water-soluble vitamin-D preparation (drisdol); the remaining infants were given vitamins A and D in an alcohol base.

In addition, all but 10 infants received vitamin E, 50 mg. three times daily. Five infants were given *d-l* alpha tocopherol acetate (ephynal acetate) beginning with the first sign of fundus abnormality. The remaining 92 infants received an aqueous dispersion of *d-l* alpha tocopherol acetate commencing with the first feeding.

* From the Department of Surgery (Ophthalmology) and the Department of Pediatrics, New York Hospital-Cornell University Medical Center. This study was supported in part by a grant from the Playtex Park Research Institute.

† Owens, W. C., and Owens, E. U.: Retrolental fibroplasia in premature infants. *Am. J. Ophth.*, 32:1 (Jan.) 1949.

This medication was continued until examinations had conclusively shown the fundus to be normal or to have consistent irreversible pathologic changes. High serum tocopherol levels were found in all instances when the determination was made. None of the infants was supplemented with iron in any form. Blood transfusions were administered when indicated by anemia.

RESULTS

Of 107 infants under observation, 90 exhibited normal fundi on the initial examination, and 42 of these continued normal throughout all subsequent examinations. In these infants, the normal premature fundus differed from the normal adult fundus in three major respects:

1. The optic disc was homogeneously pale, without its usual complement of nutrient vessels.

2. The foveal region, and particularly the macula, appeared underdeveloped, being differentiated mainly by location and by a deeper red color from the surrounding retina.

3. The periphery of the retina consistently demonstrated a pale, nonelevated, transient gray or white zone, most marked in dark-complexioned infants.

On the first examination, prior to removal from the incubator, 17 infants showed venous caliber increase and arterial tortuosity of the retinal vessels. In addition, three of these 17 infants had preretinal or vitreous hemorrhages. Venous-caliber increase and venous and arterial tortuosity were later demonstrated in an additional 48 infants.

In 54 infants, these early signs were followed by preretinal or retinal hemorrhages. In 19 of these 54 infants, no further progression of the disease was seen and the retinas returned to normal. The remaining 35 infants subsequently developed replacement of the preretinal or vitreous hemorrhages by angiofibrous proliferation. Retinal detachments followed in 27.

It is interesting to note that in only one infant were angiofibrous proliferation and

retinal detachment observed without antecedent hemorrhage. Prior to an unavoidable lapse of 18 days in our observations he exhibited marked vessel changes. Subsequently he exhibited angiofibrous proliferation and early retinal detachment.

Only seven of the infants with retinal detachments regressed spontaneously. The remaining 21 retained permanent changes constituting retrolental fibroplasia in its complete or arrested form.

Bilateral complete retrolental membranes formed by fusion of the folds of a completely detached retina behind the posterior surface of the lens were observed in seven infants. The condition in the other 14 infants was arrested, without regression, at the stage of severe retinal detachment and these detachments were retained as residuals of the disease.

From these observations we feel that the pathogenesis of retrolental fibroplasia may be described in five main stages:

1. A vascular stage consisting of venous-caliber increase and venous and arterial tortuosity.

2. A stage of hemorrhage usually consisting of preretinal (subhyaloid) hemorrhages. In many instances, these preretinal hemorrhages extend into the vitreous.

3. A stage of organization of the hemorrhages with the formation of fibrous bands and neovascularization.

4. The stage of retinal detachment, the

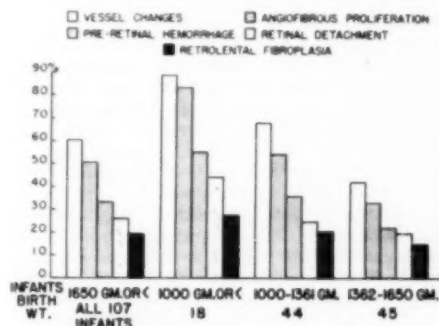


Fig. 1 (Bousquet and Laupus). Relation of fundus changes to birth weight.

elevations usually beginning at the zone of transition where the central retina appears normal and the peripheral retina is pale. In this site preretinal hemorrhages and subsequent angiofibrous proliferation appear to have a serious prognostic importance.

5. The final stage of fully developed retrolental fibroplasia with retrolental membranes formed by fusion of the peripheral folds of detached retina, and adherence of this membrane to the posterior surface of the lens.

Spontaneous regression is a prominent feature of the disease and was observed in all stages except that of complete retrolental membrane formation. Of 65 infants exhibiting pathologic ophthalmoscopic signs, only 21 eventually developed retrolental fibroplasia, and 44 ultimately exhibited normal fundi.

Of the infants in whom the process halted short of its usual severe finale but failed to regress, several exhibited peculiar retinal folds not unlike so-called congenital retinal folds or septa. Others exhibited peripheral fibrous strands and retinal detachments, which in their present state do not preclude good vision, but remain as a constant threat.

Neither persistence of the hyaloid artery tunica vasculosa lentis system nor "retinal exudation" was observed in any of the subjects.

Evidence of bleeding into the skin, the subcutaneous tissue, and the visceral organs was absent in all infants. Fourteen determi-

nations of the prothrombin time in 11 of the 54 infants with intraocular hemorrhage ranged from 64 percent to more than 100 percent of adult normal. Platelet counts on the same infants were similarly within normal limits.

Late sequelae, such as microphthalmos, posterior synechias and/or flat anterior chambers, glaucoma, and other secondary changes are not considered in this report.

Certain, as yet unanswered, questions arise in view of these observations.

Why is the vascular process limited, if it is limited, to the retinal vessels? Why is the small premature infant more susceptible to retinal hemorrhagic disease?

What role, if any, do the newer techniques for preserving the lives of these premature infants play? Is the length of stay in the incubator, the oxygen concentration of the incubator air, or the duration of oxygen therapy of any importance?

Does the diet, including vitamins other than vitamin E, have any relationship to the disease?

Will pituitary adrenocorticotrophic hormone (ACTH) live up to its early promise in the treatment of this disease?

Must retrolental fibroplasia be regarded as a necessary concomitant to the increased survival rate of the small premature infant? We are at present engaged in evaluating some of these factors.

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DISCUSSION

DR. FREDERICK H. VERHOEFF (Boston): I am not going to discuss this particular paper because, while I have some ideas on the subject, my evidence is too inconclusive for me to say anything about it; but I think you might be interested in some comments on the history of this condition.

You know that Dr. Terry was the first one to establish the fact that this disease of premature infants is an entity, but you probably do not know what caused him to begin this study and also who it was who was responsible for his being wrong in his ideas as to the nature of the condition.

The patient in the first historically important case of this kind was referred to me by Dr. Paul Chandler, on the question of whether it was a case of retinoblastoma. I made a diagnosis of persistent

fibrovascular sheath of the lens and noted that it was the first case of the kind that I had ever seen in a premature infant and also the first bilateral case. It had characteristics that I had heretofore found to be quite conclusive—fingerlike processes at the periphery coming out of this tissue behind the lens.

A day or two later Dr. Chandler called me up and said he wanted me to come over to the hospital to see a patient that Dr. Terry was about to operate upon for congenital cataract. This case showed exactly the same features as the other case. Here were two cases, both in premature infants and both bilateral seen within 48 hours. This was the beginning of the story of retrolental fibroplasia.

Dr. Chandler and Dr. Terry unfortunately accepted my explanation of the condition, and Dr. Terry never did find out that I was completely wrong about it. He died without knowing that the condition was not persistent fibrovascular sheath. He didn't like this name so he devised the term "retrolental fibroplasia." I didn't like that name because I thought the other was better, although not perfect for the supposed condition.

We still have the name "persistent fibrovascular sheath" but now it does not mean the same thing as retrolental fibroplasia. Since we must have some name for this condition, we may as well call it retrolental fibroplasia until we know more about it.

Dr. Heath will now open the discussion of the paper.

DR. PARKER HEATH (Boston): The subject of retrolental fibroplasia has had many reports from clinical studies but relatively little has been reported on its pathology or its histopathology until comparatively recently. Dr. Algernon Reese has reported early examples of several cases and Friedenwald and Owens and Owens have also reported on the early stages of this disease.

I think the fundamental morphologic findings that are of value have to come from the early stages, because the late manifestations of the disease are nonspecific. What are the early findings? There may be some disagreement in detail but I think that, by and large, the early stages as reported by the doctors mentioned, and also from our laboratory, are fairly well in agreement.

The early stages seem to be the formation of neovascular tissue in the retina at the ora. With this there is, as an antecedent to this, a certain amount of edema and this edema is exaggerated in some cases disrupting the tissue and forcing it apart. It occurs in a zone of the eye which is showing the greatest growth apparently and has the greatest variability in cellular activity and the least differentiation. These changes are not found elsewhere in the retina in the early cases.

The hemorrhage, as such, in earliest stages does not seem to be particularly significant. Hemorrhage is an incident in the being-born process of every infant, subject to the moulding of the birth canal. These hemorrhages are nonspecific, random in disposition, and are readily absorbed; but this is not true of the hemorrhage when it does occur in the ora in connection with a heavy protein-rich edema.

We have found that neovascular tissue at the ora in excessive degrees extends into the vitreous. It is only when the vitreous becomes involved that the process goes on to one of its subsequent sequelae, such as the retraction syndrome at the nervehead, formation of retinal stalks, or separation of the retina. So, we think that the earliest changes are due to some vascular leak associated with vascular proliferation, at the moment of unknown etiology. This occurs at the ora primarily and those changes which are seen later clinically, with the ophthalmoscope, are mostly secondary manifestations as the result of the organization of the vitreous.

The last stages of this disease are variations in the pathology of repair and atrophy.

If the earliest stages, then, are only seen microscopically, and I believe this is the case, I think that the investigations of the future are going to be concerned with vascular permeability and proliferation in prematurity controlled by histopathologic methods.

DR. HAROLD FALLS (Ann Arbor, Michigan): Recently we have undertaken some embryologic studies on the five-to-six-month-old fetus eye, particularly devoted to the pars ciliaris. This zone undergoes, during this period, rather rapid differentiation as has already been emphasized by Dr. Parker Heath. The ciliary body is incompletely developed, as well as its blood supply. It is most interesting to note that the peripheral retina lays over the pars ciliaris at this stage of development.

It is, consequently, my belief that retrolental fibroplasia is the result of an uncontrolled neovascularization of the retina provoked by the underlying undeveloped ciliary body, the neovascularization of the retina being an attempt to supply the unprepared ciliary body with its needed oxygen and nutrition that it cannot supply itself.

DR. JONAS S. FRIEDENWALD (Baltimore): I would like to agree with Dr. Parker Heath in his description of the early stages of the disease and try to make somewhat more specific the particular question which the essayist has raised as to the role of hemorrhage in the development of the intraocular lesion.

As Dr. Heath has pointed out, there are several sets of eyes that have been examined at an early age, in the early stage of the disease, when the disease process is still limited to the retina, and a characteristic lesion was found in those eyes characterized by intense capillary proliferation in tufts and globular masses. We have to ask ourselves, in the first place, do hemorrhage and edema occur in relation to these intraretinal stages of the disease and, if so, do they precede or follow this vascular proliferation?

In our series, we have found a limited number of minute capillary petechial hemorrhages in the retina in these early stages but we have not been able to convince ourselves that either the retinal hemorrhages or the retinal edema necessarily precede the capillary proliferation. They may, but it is extremely difficult in histologic sections to tell what comes first and what comes second.

In a later stage of the disease, the blood vessels begin to proliferate from the retina into the vitreous. In that stage, in our series, we find quite uniformly the presence of hemorrhages in the vitreous, and that is, I think, in strong agreement with the clinical findings presented in the present paper and suggests quite strongly that these hemorrhages perhaps from diseased vessels in the retina—no doubt from diseased vessels in the retina—are responsible for the proliferation into the vitreous.

In a discussion of the paper which we presented

last week at the American Ophthalmological Society, Dr. Reese made, I think, a very astute point; namely, that the blood vessels which come out of the retina into the vitreous and form a pretty characteristic picture of retinitis proliferans, do not necessarily arise from those specific areas in the retina where the most abundant capillary proliferation has previously existed or where it is simultaneously found.

Consequently, one has to assume that, in addition to whatever the factor is that leads to the capillary proliferation in the retina, some extra factor has to arise in the disease to account for the capillary proliferation from the retina into the vitreous. The two processes may be quite clearly connected.

It may be that, from these diseased retinal proliferating capillaries, hemorrhages break into the vitreous and that, from wherever the vessel is

closest to the hemorrhage, proliferation takes place into the vitreous, not necessarily related to the preëxisting retinal capillary proliferation.

That makes the thing somewhat more complicated but also would help to explain the fact that something rather radical happens in these cases up to the time of preretinal hemorrhages and preretinal vascular proliferation. Before that the disease is self-limited and can regress. After that has happened, a much more severe process is involved, generally leading to permanent damage.

DR. FRANKLYN P. BOUSQUET (closing): I would like to thank the discussers for their kind words. There is one point that perhaps I did not make quite clear in the paper, that these were not birth hemorrhages. In all but one instance, the fundi showed no hemorrhage on initial ophthalmoscopic examinations.

DEVELOPMENT OF DIABETIC CATARACTS*

JOHN W. PATTERSON, M.D.
Cleveland, Ohio

In treating a diabetic patient today, interest centers around the complications that are associated with or result from the diabetes. One of the complications of diabetes is cataract. Because of its appearance, diabetic cataract is also known as snowflake cataract. It occurs in young diabetics and is almost always bilateral.

Although snowflake cataract is the typical cataract found in young diabetics, it is not limited to this disease. The cataracts resulting from parathyroid deficiency, scleroderma, and myotonic dystrophy are reported to be indistinguishable from those found in young diabetics.¹

In recent surveys of young diabetic patients, cataracts have been found in three to 16 percent of those examined.¹⁻³ This relationship of cataract to diabetes has also been observed in the experimental animal.^{4, 5}

If one wishes to study the mechanism by which diabetic cataracts are formed, it is necessary that the work be done on animals so that conditions may be carefully controlled. Diabetes may be produced in animals by surgically removing the pancreas,

which is not a simple procedure, or by the injection of diabetogenic drugs.

Dunn, Sheehan, and McLetchie⁶ discovered, in 1943, that the injection of alloxan in animals selectively destroyed the beta cells of the islets of Langerhans with resultant diabetes. This procedure not only is simple but it also has the advantage of not destroying the alpha cells of the islets and the acinar tissue of the pancreas. Since the secretion of the alpha cells influences carbohydrate metabolism by producing a hyperglycemic factor, it is desirable to maintain these cells so that the resulting diabetes will be more like that found in humans.

More recently, it has been demonstrated that the reversibly oxidized form of vitamin C, dehydroascorbic acid, produces a diabetes similar to that which follows the injection of alloxan.⁷ The rats used in this study had diabetes which was produced by the injection of these drugs.

Before studying the mechanism of diabetic cataract formation, it is necessary to know something about the normal occurrence of cataracts in diabetes. This report deals largely with this phase of the problem, and is an attempt to relate two things—the sever-

* From the Department of Anatomy, School of Medicine, Western Reserve University.

ity of diabetes and the time required for cataract formation.

Diabetes is characterized by polyuria, glucosuria, polyphagia, polydipsia, hyperglycemia, and the failure to gain weight. These signs of diabetes vary with the severity of the disease and roughly parallel each other.* Any one of them might, therefore, be selected as a basis for quantitating the severity of diabetes.

The hyperglycemia of diabetic rats varies slightly from week to week but, when these variations are deemphasized by averaging the blood-sugar values at four-week intervals, the hyperglycemia is relatively constant for months.

This fact is particularly striking when the results obtained on 17 rats are incorporated in a single graph. Over a period of seven months the blood-sugar values fell between 360 and 400 mg. per 100 cc. of blood (fig. 1). The average of many weekly blood-sugar values on a single rat therefore serves as a useful measure of the severity of diabetes.

Diabetic cataracts in rats develop through certain stages. At first vacuoles are observed around the periphery of the lens. Later fine crystalline opacities develop centrally, and still later the lens becomes opaque. The last of these changes is readily seen in the albino rat with the unaided eye. If the eyes are observed at weekly intervals this change is definite and serves as a good end-point for determining the time required for cataract formation.

Certain qualitative observations have been made regarding the relationship of the severity of diabetes to the time of cataract occurrence. Those rats with high blood-sugar values developed cataracts in eight to 10 weeks and both eyes were involved at approximately the same time. Those rats with low blood-sugar values developed cataracts more slowly and the lesion was sometimes unilateral or developed in the second eye only after several weeks had elapsed.

In order to obtain a more quantitative relationship between the severity of diabetes

and the time required for cataract formation, a spot diagram was made with these two characteristics plotted against each other (fig. 2). The points were not arranged in a straight line but followed some type of curve.

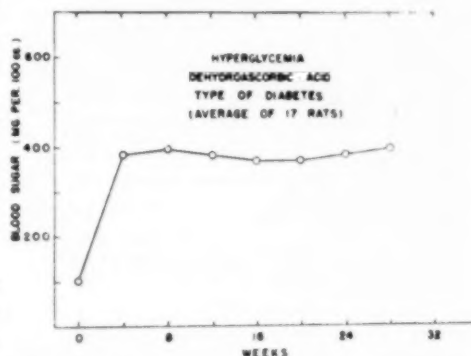


Fig. 1 (Patterson). Over a period of seven months the blood-sugar values fell between 360 and 400 mg. per 100 cc. of blood.

After trying to fit several common curves to the points, it was found that a hyperbola gave the best fit. Two empirically determined hyperbolas enclosed 90 percent of the points on the graph. With the aid of the biostatisticians a mean hyperbola was calculated by the method of least squares. This method gives equal weighting to each point in arriving at the final equation.

The calculated equation was $(x-5.7)(y-225) = 1,276$, where x and y represent the time in weeks and the blood sugar in mg./100 cc. of blood respectively (fig. 3). This equation indicated that cataracts should not appear before the week ending on day 40 and should not occur with blood-sugar values of less than 225 mg./100 cc. because these were the limiting values which the curve approached along each of the axes.

The time required for diabetic cataract formation was thus related to hyperglycemia. If these cataracts were due to the diabetes and independent of the diabetogenic agent used, then insulin should prevent cataract formation.

Rats with blood-sugar values between 400 and 600 mg./100 cc., as determined by four blood-sugar tests during the second week of diabetes, were given daily injections of protamine zinc insulin. To obtain blood-sugar

merely indicates that the diabetes must be of this severity before cataracts develop. However, it is interesting to note that this value is approximately that at which the

TABLE 1
EFFECT OF INSULIN ON DIABETIC
CATARACT FORMATION

	Controls	Insulin
Number of rats	13	7
Average blood sugar, mg./100 cc.	464	494
Cataracts, weeks	10 \pm 2.1*	None at 27 weeks

* One standard deviation.

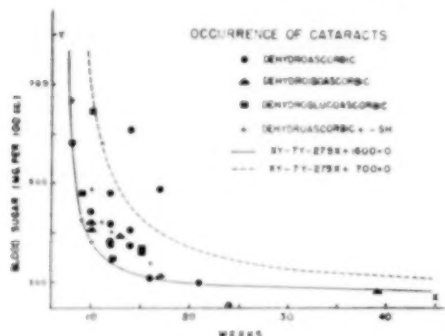


Fig. 2 (Patterson). Diagram correlating the severity of diabetes and time required for cataract formation.

values below 250 mg./100 cc. 24 hours after the last injection of insulin, it was necessary to give 10 to 12 units per kg. per day.

Control rats with blood-sugar values in the same range developed cataracts in 10

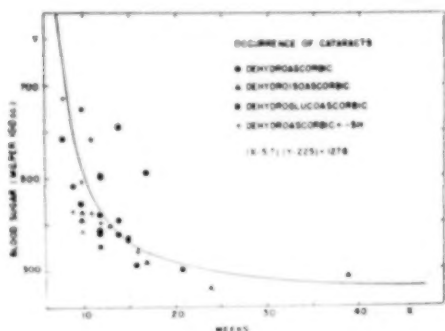


Fig. 3 (Patterson). Diagram showing relationship between hyperglycemia and time required for cataract formation.

weeks with a standard deviation of 2.1 weeks. Insulin-treated rats, however, had clear lenses, as seen with the ophthalmoscope, six months after alloxan was injected to produce diabetes (table 1).

The minimum blood sugar for diabetic cataract formation was 225 mg./100 cc. This

renal tubular reabsorption mechanisms for glucose become saturated.

Galactose cataracts are morphologically the same as diabetic cataracts.⁹ In order to produce these cataracts, galactose must be spilled in the urine.^{10, 11} This again indicates a saturation of the tubular reabsorption mechanisms of the kidney. These facts point to the kidney as a possible factor in the etiology of diabetic and galactose cataracts.

It is not difficult to postulate a mechanism whereby the kidney may be involved. Common enzyme pathways for tubular absorption are known to exist. For instance, the reabsorption not only of glucose but also galactose and xylose, the other sugars capable of producing cataracts, is prevented by the metabolic poison, phlorizin.^{12, 13}

If some other essential metabolite shares a common pathway with these sugars and the pathway is saturated by one of these sugars, then this metabolite will not be reabsorbed but will be lost in the urine with a resultant deficiency.

Deficiencies of riboflavin,¹⁴ amino acids,^{15, 16} and parathyroid hormone,¹⁷ are known to cause cataracts. Riboflavin is not

TABLE 2
SERUM INORGANIC PHOSPHORUS mg./100 cc.

Normal rats (10)	7.6 \pm 0.6*
Diabetic rats with cataracts (5)	5.7 \pm 0.3*
P < 0.0001	

* One standard deviation.

depleted abnormally rapidly in diabetics¹⁷ and, although amino acids are lost excessively in uncontrolled diabetes,^{19,20} the fault does not lie in the kidney since the blood level of amino acids is also raised.²⁰

The biochemical mechanism by which parathyroid hormone produces its effects is not known, but it is known that the loss of this hormone produces marked changes in calcium and phosphorus metabolism. Diabetes also alters calcium and phosphorus metabolism.

Following the production of diabetes, the serum alkaline phosphatase increases and may rise to three times the normal level.²¹ Although the serum inorganic phosphate

level is normal at first it is definitely decreased at the time cataracts occur (table 2).

These changes in diabetes are suggestive of rickets. The cataracts of rickets, however, are better correlated with signs of parathyroid deficiency, such as tetany and hypoplasia of the teeth, than they are with rickets.²² The parathyroid glands of chronic diabetic patients²³ and animals²⁴ have been described as being small and degenerated.

These relationships of diabetes to parathyroid deficiency, plus the fact that they produce morphologically similar cataracts, suggest that they may result from a common metabolic deficiency.

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DISCUSSION

DR. LUDWIG VON SALLMANN (New York): First, I would like to know the particular technique which Dr. Patterson has used to produce the alloxan cataract in rats. Secondly, I should like to ask him about the statistical validity of his findings, especially in regard to the mathematical correlation of the levels of sugar in the blood and the onset of the cataract.

Dr. Patterson referred to the similarity of the alloxan cataract to that produced by galactose. Dr. Dische and Miss Borenfreund of our Research Department have worked on this type of cataract

and I was permitted to examine the eyes of these rats biomicroscopically. I hope that Dr. Dische will be able to say a few words about his results.

The observations on galactose cataract are in agreement with the description given by Dr. Patterson on the alloxan animals in respect to the appearance of vacuoles in the anterior cortex and especially at the periphery of this portion of the lens. However, there were great differences in the appearance of the cataract between the right and the left eye in many animals and there was no clear correlation of the galactose level in the blood

with either the onset nor the severity of the cataract.

Dr. Patterson referred to these differences between the right and the left eye of individual animals in the group in which the glucose level was low. I wonder whether he would express his opinion on the cause of this difference.

Dr. Patterson spoke of the lowering of the level of the inorganic phosphorus in the blood of the alloxan animals and suggested that this change in the mineral content has something to do with the formation of the cataract. May I ask whether the content of inorganic phosphorus was determined in the lenses of these rats?

DR. DAVID COGAN (Boston): I would just like to note some minor differences of opinion or interpretation which in no way mitigate against Dr. Patterson's general thesis. First, his statement that the cataract in myotonia and in hypoparathyroidism are similar to the snowflake type of cataract in the young diabetic.

I am certainly limited in the number of observation which I have had occasion to make—I don't suppose I have seen more than a dozen hypoparathyroid cataracts and probably not more than half a dozen cataracts in myotonia, but I have the impression they are distinctly different.

Those in myotonia and hypoparathyroidism seem to me to be cataracts that, in their early stages, consisted of subcapsular minute rods, some of them brownish, and little dots and quite different from the coarse snowflakes which occur in the young diabetics and which are seen not only immediately subcapsular but for a millimeter or two into the cortex. I would be interested in having Dr. Patterson straighten me out on this.

The other minor discrepancy in my understanding and his is the suggestion that these cataracts are like hypoparathyroidism in the fact that the phosphate is lower. It is my understanding that the serum phosphate is elevated in hypoparathyroidism and calcium is lowered; indeed if I cite the Albright thesis properly, the renal sparing of phosphate is the prime cause of the calcium disturbance; that is, there is an excess of phosphate rather than a deficiency in hypoparathyroidism.

DR. JOHN W. PATTERSON (closing). First to answer some of the questions raised by Dr. von Sallmann: The technique used for the production of alloxan diabetes was the intravenous injection of 40 mg. per kg. of alloxan monohydrate.

I do not know of a statistical method by which one can prove that a particular curve is correct. One may measure the distances of the various points from the proposed curve and calculate their standard deviation. If this is done for several common curves then the curve with the lowest standard deviation may be chosen as the best fit. The equation for this curve is then a first approximation for describing the relationship existing between hyperglycemia and the time required for cataract formation.

We have suggested that galactose cataracts may result from the same etiologic factors that are involved in the production of diabetic cataracts. In partial support of this thesis, it has been pointed out that the morphology of galactose and diabetic cataracts is the same.

This statement is based on the literature and not on personal experience. Dr. Buschke at one time presented a classification of cataracts in rats. This classification was based on morphology and galactose and diabetic cataracts were grouped together.

As Dr. von Sallmann has pointed out, there is some variation in the morphology of developing galactose cataracts. This is also true of diabetic cataracts. However, it would seem that galactose and diabetic cataracts are sufficiently alike so that one may postulate a similar etiology.

As to the unilateral development of cataracts, I feel that this is probably a matter of degree. Although a cataract may mature in one lens first, the second lens is not free from change. Ophthalmoscopic examination of the second lens will reveal that a cataract is also developing there but at a slower rate. Why there should be this variation between eyes I do not know. Either the right or left eye may be the first to develop a mature cataract. I suppose that we would have to say that it is a matter of biologic variation.

I have not done phosphorus levels in the lens.

In response to Dr. Cogan's question I must again fall back on the literature. In a paper by Waite and Beetham the statement is made that the cataract of juvenile diabetics is indistinguishable from that found in parathyroid deficiency, scleroderma, and myotonic dystrophy. I have not had any experience with these cataracts. However, allowing for certain variations, it would seem that they are enough alike morphologically to suggest that they may have a common etiologic basis.

Dr. Cogan is perfectly correct in pointing out that the serum phosphorus is high in parathyroid deficiency, whereas, in our rats the serum phosphorus was low. This low value for serum phosphorus which follows an increase in the alkaline phosphatase is suggestive of rickets.

Animals with rickets may develop cataracts. However, as Dr. Bellows has brought out in his book on *Cataracts and Anomalies of the Lens*, the cataracts associated with rickets are better correlated with the signs of parathyroid deficiency, such as tetany and hypoplasia of the teeth, than they are with rickets per se. Thus, although the serum phosphorus levels are different in rickets and parathyroid deficiency there must be other factors that are common to both conditions.

It is thought that the low serum calcium which is associated with parathyroid deficiency as well as with certain stages of rickets may be the common factor that is responsible for cataract development. It is interesting to note that cataracts are frequently associated with healing rickets. At this time, calcium is being taken up by the skeleton and the serum level may become quite low.

ANTIBIOTIC-PRODUCING BACTERIA OF THE OCULAR FLORA*

SEYMOUR P. HALBERT, M.D., AND LOIS S. SWICK, B.S.
New York

The fundamental mechanisms involved in the recovery from bacterial conjunctivitis are not well understood. These superficial infections occur in a tissue where there normally exists a mixed bacterial population; and they are very rarely associated with significant deeper tissue invasion.

Shigella infection of humans (bacillary dysentery) is quite similar to bacterial conjunctivitis in these two basic and important respects. In this disease, recent studies¹⁻³ have suggested that the usual mechanism of antibody formation is not important in the recovery or resistance processes.

Other observations⁴⁻⁹ have revealed that many strains of microorganisms normally living in the intestinal tract are capable of producing antibiotic substances. Surprisingly large numbers of such strains have been found, and very high percentages of individuals carry them. In several instances, the entire course of dysentery infections have been followed.¹⁰

In these patients, striking increases in the concentrations of such antibiotic-producing organisms were found to occur within several days after the onset of the infection. In addition, in survey observations, individuals found to be infected with *Shigella* organisms were more likely to be carrying antibiotic-producing coliform strains. These data, and others, therefore suggest that antibiotic-producing bacteria in the intestinal tract may play a role in the recovery from dysentery infections.

Because of these observations, and the two basic similarities between bacterial conjunctivitis and the intestinal infections already pointed out, it was felt of importance to

carry out studies designed to reveal whether phenomena analogous to those described as occurring in the intestinal tract, also occur in the ocular flora.

Since staphylococci are among the most constant organisms of the eye flora, observations indicating that some strains of the staphylococcus family can produce antibiotics^{11, 12, 23} lent support to this possibility.

The following report is concerned with preliminary observations as to the existence of antibiotic-producing organisms in the conjunctival and lid flora of humans.

MATERIALS AND METHODS

The patients examined in this study were inmates of Letchworth Village, a New York state institution for the feeble-minded.† They were all adult males, and resided in two cottages. Approximately one half of the patients of each group had conjunctivitis at the time of examination.

Combined cultures of the conjunctivas and lids of the left eyes were obtained with sterile swabs moistened with proteose-peptone No. 3 (Difco) broth. These were streaked onto four plates containing either proteose No. 3 agar (Difco), five-percent human plasma agar or five-percent human blood agar made with the same medium. The inoculations were made so that one area of each plate would be likely to show rather dispersed growth.

All of the cultures were incubated at 37°C. for 24 hours. At this time, sample colonies were picked to fresh media, and the numbers of each morphologic type estimated. The

† The authors are deeply indebted to Dr. Harry C. Storrs, director of Letchworth Village for his generous cooperation in making the patients available for study. Grateful thanks are also given Dr. L. von Sallmann, Dr. R. L. Wiggins, and Dr. D. Locatcher-Khorazo for assistance and advice concerning the clinical aspects of this problem.

* From the Departments of Ophthalmology and Bacteriology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital.



Fig. 1 (Halbert and Swick). *Staphylococcus albus* No. 7-6 spray-seeded onto blood agar after 48-hour incubation of original inoculum from one patient. The arrows point to highly active antibiotic-producing organisms.



Fig. 2 (Halbert and Swick). The same procedure as described in Figure 1 carried out on plasma agar from the inoculum from another patient. The arrows point to slightly active antibiotic-producing organisms.



Fig. 3 (Halbert and Swick). The same procedure as described in Figure 1 carried out on plasma agar from the inoculum from a third patient. The arrows point to slightly active antibiotic-producing organisms.

cultures were then further incubated at 37°C. for 24 hours, and the specimens of each patient were then divided into groups of two each.

The surfaces of these plates were then sprayed with broth suspensions of either of two strains of staphylococci isolated from this same group of patients. They were found in preliminary tests to be susceptible to these types of antibiotic-producing organisms. The two strains most commonly used were No. 7-6 and No. 15-1, which have been tentatively identified as a *Staphylococcus albus* and a *Staphylococcus aureus*, respectively.

The method used in spraying this indicator culture inoculum was a slight modification of that described by Stansly.¹³ After spray seeding, the plates were further incubated at 37°C. for another 24 hours, and then examined for the presence of colonies which were surrounded by inhibition zones. When such antibiotic-producing organisms were noted, estimates were made of the number of active and nonactive strains in the area of the plate where only well-isolated colonies were present.

Samples of the active strains were then re-picked onto fresh medium, and later retested for inhibitory activity against the same susceptible indicator strains by the simultaneous inoculation method on proteose No. 3 agar (Difco) used in other studies.⁷

Only those that were active by this technique were included in the final tabulations. In some instances, random samples of 20 organisms were picked from the original plates after 24 hours, and later retested by the simultaneous technique already described.

RESULTS

Significant numbers of antibiotic-producing organisms have been found in the eye flora. In many respects, the observations are analogous to those noted in the gastro-intestinal tract. The type of results to be seen on the original plates after spray seeding

with the indicator strains are shown in Figures 1, 2, and 3.

It may be seen in these that some strains produce large clean-cut zones of inhibition under these circumstances, while others produce smaller, often rather poorly defined zones. It is of a good deal of interest to note that very often active strains show no colonial differences from neighboring colonies that do not produce antibiotics. Similar lack of such differentiation was noted among the coliform flora of the intestinal tract.⁷

When these active organisms are replanted to fresh medium, and examined by the simultaneous inoculation method with the same indicator strains, the differences in the types of activity are more clearly apparent. Some strains produce large clean-cut zones of complete inhibition; others produce small clean-cut zones of complete inhibition; others produce varying-size zones of different degrees of partial inhibition; and others produce no change at all in the surrounding colonies.

Examples of these types of results are shown in Figure 4. Organisms No. 146-7 and No. 145-10 produced complete inhibition of growth up to 6.4 mm. from the edge of the active colony when tested against *Staphylococcus aureus* No. 15-1. Strains No. 110-6 and No. 81-5 showed complete inhibition zones of about 3.0 mm., while No. 133-3 and No. 121-6 showed very small zones of partial inhibition.

In Figure 5, are shown several examples of other types of partial inhibition that have been noted. Strains No. 266-6 and No. 269-5 when tested against *Staphylococcus albus* No. 7-6 showed rather large zones of partial inhibition. Although not clearly apparent in Figure 5, the incompleteness of the inhibition by these strains under these circumstances was revealed by the presence of very stunted and almost transparent colonies in the zone of inhibition up to the edge of the active test organisms.

This is revealed very strikingly in Figure

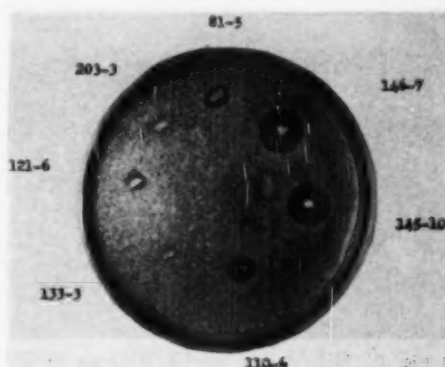
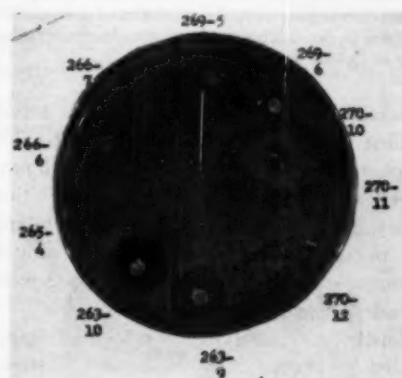
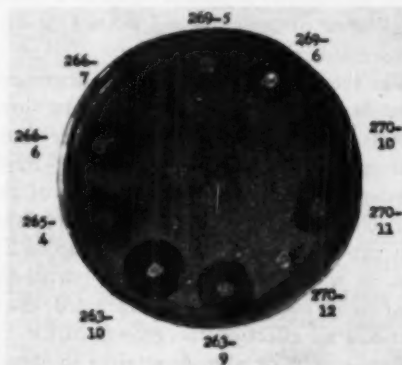


Fig. 4 (Halbert and Swick). Retests of isolated antibiotic-producing strains against *Staphylococcus aureus* No. 15-1.



vs. No. 15-1



vs. No. 7-6

Fig. 5 (Halbert and Swick). Comparison of the antibiotic activity of a group of strains against two staphylococci.

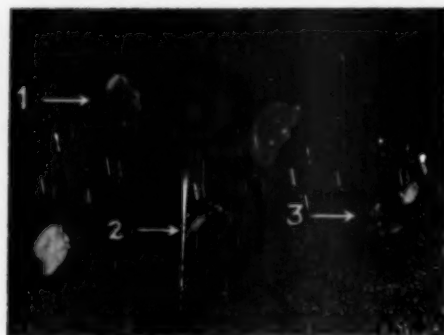


Fig. 6 (Halbert and Swick). Example of the partial inhibition produced by some strains of antibiotic-producers. All three organisms indicated by the arrows produced exactly the same kind of inhibition. Because of the direction of the light in taking the photograph, the stunted and transparent colonies in the inhibition zones are clearly revealed only in Colony 3.

6, which show five other test strains acting against *Staphylococcus albus* No. 7-6. The three strains designated by the arrows all produced *exactly* the same type of inhibition zones, but the direction of the light in taking the photograph was such that the stunted colonies in the inhibition zone of No. 3 were revealed clearly.

Lastly, another type of inhibition is revealed in Figure 5 by the action of strain No. 269-5 against *Staphylococcus aureus* No. 15-1. This zone was characterized by a rather large area of very poorly defined or circumscribed inhibition.

For the sake of tabulation, the organisms have been arbitrarily classified into three groups. The *highly* active strains are those that produced complete inhibition zones greater than 2.5 mm. from the edge of the test colony. *Slightly* active strains were those that produced complete inhibition up to 2.5 mm. in width, or any degree of partial inhibition. *Nonactive* strains included those that had no effect on the growth of the indicator strains or were themselves inhibited.

It may be mentioned here that the antibiotic-producing strains have been found to

maintain their activity over periods of up to a year after numerous transfers on artificial media.

The numbers of individuals carrying such organisms in their flora is surprisingly large. In the samples obtained on one visit, for example, 24 of the 40 individuals (60 percent) revealed the presence of active strains. Of these, nine of the group (20 percent) showed highly active organisms; 19 possessed slightly active strains (50 percent); and four had both types present.

In a sample obtained from another cottage, 36 of the 40 individuals (90 percent) harbored such active strains. Of these, six of the 40 (15 percent) revealed the presence of highly active organisms; 35 (85 percent) slightly active ones; and five (12 percent) both types.

The concentrations of active strains in the flora of the patients varied very widely. In some patients they were very rare (for example, 1:100, 1:30, or 1:200, and so forth, countable organisms); in others active organisms were more numerous (for example, 15:60, 3:100, 4:16, 6:75, and so forth countable organisms); and in occasional patients they were predominating (for example, 27:30, 100:150 countable organisms).

Antibiotic-producers were found both in normal and infected eyes, but the data thus far are insufficient for detailed analysis.

Estimates were made of the percentage of active strains present. In one group of 40 patients, approximately 1,500 strains could be counted in the dispersed areas of the original plates. Of these 14 (0.9 percent) proved to be highly active, and 163 (10.8 percent) were slightly active.

Tests made of this same group of cultures by random sampling methods showed that of 800 strains tested, 0.1 percent were highly active, and 15.4 percent slightly active. It is of some interest that Jennings and Sharp¹¹ reported that about 10 percent of the 205 strains of staphylococci from

various sources that they tested possessed antibiotic-producing activity.

The vast majority of the organisms observed here were of the genus *Micrococcus* (*Staphylococcus*). Thus, of 174 sample strains (approximately equal numbers of active and nonactive organisms) examined by the Gram stain in one sampling period, 167 were of the staphylococcus family. Five were streptococci, one a diphtheroid, and another a Gram-positive rod in chains. The same pattern of distribution was apparent in other culture periods.

Thus, the bulk of the antibiotic producers were staphylococcal, although occasional active streptococci and diphtheroids were observed. It may be mentioned that, in most instances, the activity of these organisms was not usually affected by the presence of 10-percent human blood or plasma in the medium.

Although the antibacterial spectra of samples of active strains have not been carried out as yet, a fairly large number of organisms (mostly of the staphylococcal family) have been tested for susceptibility to a sample of these strains in the preliminary search for sensitive indicator organisms.

All of the bacteria tested were isolated from the eye flora of the subjects under study at Letchworth Village. There was a very wide variation in the susceptibility of these strains to the samples of antibiotic-producers.

A suggestion of this is shown in Figure 5 where, for example, strains No. 266-6 and No. 269-5 showed quite different effects on the indicator organisms No. 7-6 and No. 15-1. In some instances, not shown here, an active strain might affect one of the indicators and not the other.

The high degree of strain specificity involved in the susceptibility to these antibiotics has been demonstrated in some detail by Fredericq¹² with a small group of antibiotic-producing staphylococci. This same limited type of activity and susceptibility has been

amply shown to be the rule in the *Escherichia coli* group of antibiotics.^{6, 7, 14}

Preliminary tests with regard to the production and characterization of the antibiotics have been carried out with a small number of strains.* The same methods have been employed that were successfully used with *E. coli* antibiotics. Organisms were grown 24 or 48 hours on the surface of proteose No. 3 agar medium with only 0.5-percent agar content.

At that time, the plates were rapidly frozen in pulverized solid carbon dioxide, and then thawed. The fluid that was then obtained was centrifuged free of cells, and the clear supernate sterilized by heating at 63°C. for one-half hour. These crude liquors, in a number of instances, have shown antibiotic activity comparable to that seen with antibiotic-producing coliform strains of the intestinal tract.



Fig. 7 (Halbert and Swick). Antibiotic activity of some crude supernates from several active staphylococci tested against strain No. 15-1.

As an example of the type of results obtained in tests against *Staphylococcus aureus* No. 15-1, Figure 7 shows the inhibiting activity of supernates from five strains of staphylococci isolated from different patients

* On the basis of catalase activity, occasional strains revealed inhibition zones which were probably due to H_2O_2 production.¹¹ These strains were not considered in the present study.



Fig. 8 (Halbert and Swick). "Spontaneous" appearance of inhibiting activity in the original streak from the eye swab of a patient.

of this group. The largest zone, by the crude antibiotic of *Staphylococcus albus* No. 303-3, was 8.0 mm. in width (from the edge of the well in the agar to the edge of normal growth of the substrate organism).

Strains No. 207-5 and No. 218-4 produced zones of partial inhibition when tested with the living organism system, and it is of interest that the supernates produced very poorly defined zones of "inhibition" of some size, which are only faintly visible in the photograph. Further detailed studies are under way to determine the chemical and physical characteristics of samples of these antibiotics.

In four instances out of 246 samplings from 80 patients, the following type of related phenomenon has been observed. On the original plates from these patients, one type of organism has been very predominant, and developed as an almost uniform and confluent growth in the crowded areas of the plates. Interspersed in these areas were occasional to fairly numerous colonies which had produced areas of inhibition about themselves of the predominant bacterial species present in the flora. Figure 8 shows an example of this type of reaction.

Attempts to isolate and characterize the

organisms involved have been incomplete, but in one instance the inhibiting strain was a *Staphylococcus albus* and the inhibited strain was tentatively identified as *Hemophilus influenza*. In another instance, the inhibiting strain was also a *Staphylococcus albus* strain, and the inhibited organism a *Neisseria catarrhalis*.

In future studies, it is planned to obtain culture samples at short intervals from patients who reveal such mixtures in their flora, and to observe the progressive changes in the concentrations of the organisms involved.

Dujardin-Beaumetz²⁰ has reported a very similar phenomenon occurring on a plate inoculated with nasal mucous from a patient convalescent from diphtheria. In this instance, the inhibiting organism was a *staphylococcus*, and the inhibited one a strain of *Corynebacterium diphtheriae*.

DISCUSSION

The preliminary data thus far obtained with respect to the presence of antibiotic-producing bacteria in the eye shows a remarkable analogy to the presence of such organisms in the intestinal tract. These similarities include the following findings.

1. In both situations, antibiotic-producing bacteria are quite common. They are present in many individuals. The concentrations of such organisms in the flora vary widely from individual to individual.

2. Antibiotic producers of strikingly different degrees of activity are present in both situations. Some are very potent, producing complete inhibition of susceptible organisms over wide distances on agar; some produce small zones of complete inhibition and others produce varying size zones of partial inhibition of varying degrees. In both tissues, several types of antibiotic-producers may be found in the flora of the same individual.

3. The prevalence of such active strains in individuals is strikingly similar in the two tissues. Discounting the differences in the

TABLE 1
COMPARISON OF THE INCIDENCE OF ANTIBIOTIC-PRODUCING BACTERIA IN THE EYE FLORA
AND INTESTINAL TRACT OF TWO ADULT POPULATIONS

Group	Antibiotic-producing Bacteria from	Number of Individuals	Individuals With			Total Individuals with Antibiotic-producers
			Slightly* Active Strains Only	Highly Active Strains Only	Both Types	
North Carolina	Intestinal Tract	108	47 (43%)	12 (11%)	8 (7%)	67 (62%)
Letchworth Village (New York)	Eye Flora	40 (Cottage Delta)	31	0	4	35
		40 (Cottage Theta)	15	5	3	23
		80 (Total)	46 (57%)	5 (6%)	7 (9%)	58 (73%)

* The classification system in the eye flora is slightly different from that in the intestinal tract, and the methods of sampling in each series were slightly different, but the data are fairly comparable.

methods employed, Table 1 reveals the remarkable similarity in the incidence of antibiotic-producers in the eye from this adult group at Letchworth Village,* and the incidence of active coliform organisms from the intestinal tract of an adult population in North Carolina.

4. The antibiotic-producers of both tissues show a high degree of strain specificity in their antibacterial activity. Although this specificity has not been thoroughly analyzed with reference to the ocular microorganisms, these preliminary observations, and the more detailed data with a small group of strains of staphylococci examined by Fredericq,¹² strongly indicate that the antibiotic-producers of both tissues are very similar in this respect. The highly specific nature of the antibiotics of the *E. coli* group has been worked out in some detail.

5. Preliminary tests have revealed that rather potent crude antibiotic solutions can be readily obtained with a number of strains of the eye flora by the same methods that

were very often effective with the intestinal coliform organisms. Study of the chemistry of one antibiotic from a staphylococcus strain by Gardner¹⁵ has revealed a striking similarity in the chemical properties of this material with those of several antibiotics of *E. coli* strains that have been examined rather carefully.¹⁶⁻¹⁸ Further studies are under way to determine the general chemical characteristics of antibiotics from a number of strains of staphylococci from the eye flora.

6. The antibiotic-producers of both tissues usually maintain their activity in the presence of plasma proteins or blood in moderate concentrations.

7. The percentage of intestinal tract coliform strains examined that possessed activity in previous series using sampling methods varied from 11.7 percent to 24.8 percent. In the present series, preliminary estimates of the percentage of active "staphylococci" from the eye flora suggest that the value will be between five percent and 15 percent in this group. Jennings¹¹ has found an incidence of antibiotic-producers of 10 percent in a group of staphylococci studied by him.

* Subsequent observations of other groups at this institution have revealed, however, a somewhat lower incidence of active strains in this test system.

8. The antibiotic producing organisms of the gastro-intestinal tract have thus far shown the same metabolic characteristics that nonantibiotic producers reveal.⁶ Jennings¹¹ and Fredericq¹⁹ failed to find any correlation between antibiotic production and metabolic activities with the strains of staphylococci studied by each. Preliminary observations in this laboratory are in agreement with these latter investigators.

9. The antibiotic-producing capacities of these microorganisms seems to be a rather stable metabolic property. Numerous transfers of such bacteria, from both sources over long periods of time, have not usually resulted in any significant change of this attribute.

In summary, the similarities thus far revealed suggests that the bacterial population interrelationships in both tissues may be

fundamentally alike. Further investigations are being carried out to determine whether population changes of antibiotic-producing organisms in the eye take place in relation to bacterial eye infections, as seems to occur in the intestinal tract.

SUMMARY

1. Antibiotic-producing bacteria occur in the eye flora with considerable frequency.
2. The organisms are mostly of the genus *Micrococcus* ("Staphylococcus").
3. Varying degrees and types of inhibitory activity have been noted.
4. In several instances, crude antibiotic solutions have been prepared.
5. The striking analogy between the antibiotic-producing organisms of the eye and of the intestinal tract has been discussed.

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DISCUSSION

DR. HENRY F. ALLEN (Boston): The appearance of diphtheroids in the conjunctiva following acute infections of different kinds has been well known for some time. Dr. Halbert did not mention specifically whether diphtheroids were among the antibiotic producers. I have nothing to add and no experience in antibiotic-producing strains. The question, I think, which presents itself to all of us is what the practical significance of such strains would be, whether they are producing infection or preventing infection, and that is one of the questions which the essayist has left open.

DR. ALSON E. BRALEY (Iowa City): To my mind, this is a most interesting observation which has been made by Dr. Halbert and I wish to congratulate him on his observation. Antibiotic-producers have gone unobserved, obviously, by a great many of us working in bacteriology over the past years, and for that reason I appreciate the essayists' observation.

I did have a few questions to ask because I know most of these patients from Letchworth Village and their conditions very well. Many of them have a conjunctivitis and many are reasonably free of conjunctival irritation. I wanted to ask if there were more antibiotic-producers in those patients with conjunctival irritation or in those without it, with normal conjunctiva.

The second question: It appeared to me as if the staphylococci were of the old classification of

the rough variety that produced the antibiotics, or at least produced the zone of inhibition, but I think that this should be followed up very carefully and considerably more data should be collected on this material, particularly on the evidence that these antibiotic substances are polypeptides.

DR. SEYMOUR P. HALBERT (closing): With regard to the diphtheroids, Dr. Allen, we occasionally have found diphtheroids to be active in this respect. The number of diphtheroids we have noticed on the cultures from these individuals is rather sparse but may be due to the methods of cultivation that we use.

With regard to the antibiotic-producers in conjunctivitis or normal conjunctiva, Dr. Braley, we have a considerable amount of data along these lines but we have not as yet studied them statistically. The analysis of the information will take us several months and we were not able to get it ready for this meeting.

With regard to the colony growth of the antibiotic-producers, we have not noticed that these tended to be rough in colonial form. They do show most of the smooth type of colony, although occasionally some strains have been somewhat rough.

We understand quite clearly that the full significance of these organisms in infection is a difficult problem and to elucidate it will take an extensive amount of work with careful observations and controls.

POLYMYXIN IN EXPERIMENTAL OCULAR PSEUDOMONAS AERUGINOSA INFECTIONS

JOSEPH V. M. ROSS, M.D.
Berwick, Pennsylvania

Gram-negative rod eye infections are notoriously resistant to therapy. Especially is this true of *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) infections. It is generally true that, if therapy is effective for this organism, it will probably be of value for most Gram-negative infections. For this reason it was thought proper to determine if polymyxin B, an antibiotic from *B. polymyxa*, which is effective against many Gram-negative bacteria, might be of value in experimental ocular *Pseudomonas aeruginosa* infections.

METHOD OF INVESTIGATION

1. All the studies were made on rabbits' eyes. The rabbits were all bucks of the chin-chilla strain and weighed 2.5 to 3.5 kg. each.

2. The polymyxin used was lot No. P-095, N.D. #111, Aerosporin, Brand, polymyxin B (sulfate), 50 mg. vital.* The concentration used locally was 10 mg./cc. of normal saline since previous studies had shown that strengths greater than this were not tolerated well by an abraded rabbit's cornea. All drops were given every one-half hour for one week after the wounds were contaminated. For anterior-chamber injections, 0.1 cc. of 0.25 of this strength in normal saline was used once.

3. A standard corneal abrasion consisted of denudation of one fourth of the corneal surface with sterile gauze as confirmed by staining.

A standard penetrating posterior-segment wound was produced by a rapid plunge into, and immediate withdrawal from, the vitreous with a sterile 25-gauge, 0.75-inch hypodermic needle.

4. The cultures used were virile, T-4 dilu-

tions, of *Pseudomonas aeruginosa*. One drop from a standard medicine dropper was used to contaminate the corneal abrasion immediately. The sterile hypodermic needle was dipped into a culture before being plunged into the vitreous to contaminate the posterior-segment wound.

5. A lost eye was defined as that so scarred either in the anterior segment or posterior segment or both, with or without phthisis, so that such an eye, comparatively speaking, in a human would be industrially blind.

RESULTS

CONTROL EYES

Of 10 eyes with a standard corneal abrasion, contaminated, nine were lost and one moderately scarred.

Of 10 eyes in which the penetrating posterior-segment wound was contaminated, all were lost.

CORNEAL LESIONS

In 10 eyes in which polymyxin B was dropped every half hour for four doses before and after the contaminated abrasion was produced, five were lost and five moderately scarred. In 10 eyes in which the drug was applied locally within one hour of the contaminated abrasion, seven eyes were lost and three moderately scarred. When the antibiotic was used locally after two hours following the contaminated abrasion, all 10 eyes were lost.

When polymyxin B was given into the anterior chamber within one hour after the contaminated abrasion, seven eyes were lost and three were moderately scarred. A severe serofibrinous iridocyclitis resulted from the anterior-chamber injections so only one such was given in each case.

* The polymyxin used was supplied by the Burroughs Wellcome and Company, Inc., Tuckahoe, New York.

TABLE 1
CHART OF RESULTS

Method of Investigation	Number	Lost Eyes	Moderately Scarred Eyes
1. Contaminated control eyes. No therapy			
a. Corneal cases	10	9	1
b. Posterior-segment cases	10	10	—
2. Contaminated treated eyes			
a. Corneal—Polymyxin before and after	10	5	5
b. Corneal—Polymyxin within one hour	10	7	3
c. Corneal—Polymyxin plus one anterior-chamber injection	10	7	3
d. Corneal—Polymyxin after two hours	10	10	—
e. Posterior segment			

All eyes were lost regardless of time element or anterior chamber injection.

POSTERIOR SEGMENT

All eyes were lost regardless of time element or anterior-chamber injection.

CONCLUSION

Polymyxin B (lot No. P-095, N.D. #111, "Aerosporin" Brand polymyxin B [sulfate] when used in the concentrations and method

herein stipulated has little or no practical value in the therapy of eye wounds contaminated with *Pseudomonas aeruginosa*. Anterior-chamber injection is not recommended.

321 East Front Street.

The discussion of this paper will be found on page 99.

EXPERIMENTAL STUDIES ON THE EYE WITH POLYMYXIN B*

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New York

Polymyxin B is one of the group of related antibiotics obtained from the soil organism *Bacillus polymyxa*.¹ These substances have marked antibacterial activity in vitro, against Gram-negative organisms, except for strains of the genus *Proteus*.^{2,3} They have relatively little effect against Gram-positive organisms.

The clinical usefulness of polymyxin B has been limited because it has a nephrotoxic

action when administered systemically.^{2,4,28} Because local use of other antibiotics has not always been successful in controlling surface infections of the human eye due to Gram-negative bacilli, it seemed worth-while to investigate the effects on the eye of topical applications of polymyxin B.

Pseudomonas aeruginosa (pyocyaneus) was selected as the test organism because the lesions it produces in the human eye are usually of a severe type. For comparison, aureomycin, streptomycin, and circulin (Q-19) were used during various experiments. Chloramphenicol (chloromycetin) and terramycin were not employed because they have a relatively low antibiotic activity in vitro against *Pseudomonas aeruginosa*.^{5,6}

* From the Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, and the Institute of Ophthalmology of the Presbyterian Hospital. This study was supported by the Knapp Memorial Foundation. Thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Medical Science, Columbia University.

OUTLINE OF THE INVESTIGATION

The work reported here has included the following studies:

1. In vitro sensitivity tests against a large number of strains of *Pseudomonas aeruginosa* isolated from widely separated geographic areas.
2. Observations on the toxic effects of local administration of polymyxin B on the corneal epithelium.
3. Determinations of the amount of penetration of the antibiotic into rabbit eyes, following three methods of local application.
4. Preliminary in vitro experiments to test the possibility of an increased antibacterial effect using combinations of polymyxin B with each of the other three antibiotics.
5. Local treatment of experimental pyocyanus infections in rabbits' corneas.

IN VITRO SENSITIVITY TESTS

MATERIALS AND METHODS

The Aerosporin brand of polymyxin B (Lot No. p-095)* in the form of the sulphate was used in all experiments. Circulin (Q-19),† an antibiotic obtained from *Bacillus circulans*, was discovered by Murray and Tetrault⁷ and is closely related to the polymyxins in structure and biologic activity.⁸⁻¹⁰ It was received in vials of 100 mg. labelled as having been assayed at 5,000 units per mg. (presumably by the standard circulin plate assay method).⁸ The aureomycin used was the hydrochloride with sodium glycinate added, and the streptomycin was the calcium-chloride complex.

Eighty-five strains of *Pseudomonas aeruginosa* were obtained from sources‡ in England, Canada, Texas, and New York, includ-

ing stock cultures from the National Collection of Type Cultures in London and the American Type Culture Collection in Washington. One strain had been isolated from the eye of a patient with a severe infection of the cornea. Cultures were stored on agar slants under oil at refrigerator or room temperature and transferred every four to five months.¹⁰

A broth dilution test was used, in which duplicate serial twofold dilutions of the antibiotics in 0.8 cc. of nutrient broth (Difco) were made in 13 by 100-mm. test tubes. The inoculum was prepared by washing off with 0.9-percent saline the 24-hour growth of the organisms on Proteose #3 (Difco) agar slants.

The light transmission through the suspension was measured in a Klett-Summerson photo-electric colorimeter and the approximate number of viable organisms per cc. was determined from a previously prepared curve relating light transmission to plate counts.

The suspension was then diluted in nutrient broth to obtain a final concentration of about 500,000 organisms per cc. Then 0.2 cc. (100,000 organisms) of the final suspension was added to each tube. After 20 hours' incubation at 37°C., the tubes were read and the end point or minimal inhibitory concentration (M.I.C.) was taken as that tube, containing the smallest amount of the antibiotic, in which there was no visible growth.

Groups of 10 to 15 strains were tested at the same time with polymyxin B, streptomycin, and aureomycin. The circulin was not obtained until after the sensitivity tests had been done and only five strains have been tested against this antibiotic during the course of the experiments with combinations.

For each test, dilutions of the antibiotics were prepared from fresh stock solutions in saline or from stock solutions which had been stored one to two weeks in the deep freeze. The results of these tests could be reproduced so that reassays performed with more than half the strains checked within one

* Obtained through the courtesy of Dr. D. S. Searle, from Burroughs Wellcome Company, Tuckahoe, New York.

† Lot No. 8966-1 supplied in generous amounts by the Upjohn Company, Kalamazoo, Michigan.

‡ I am particularly indebted to S. T. Cowan, Dr. R. M. Shaw, Lieut. Col. Edwin J. Pulaski, and Dr. A. J. Weil for their kind help in procuring the cultures.

tube except on rare occasions. When there was a difference the minimal inhibitory concentration reported is either the one obtained most frequently or the highest value.

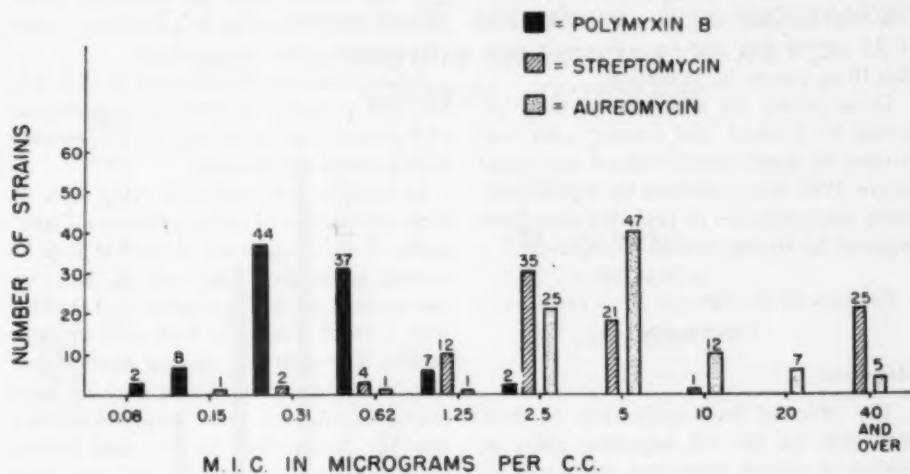
RESULTS

The distribution of the minimal inhibitory concentrations for these strains is shown in Figure 1. Under the conditions of the tests,

reports^{9,11} where broth-dilution methods were used.

Among the factors which may have contributed to the lower minimal inhibitory concentrations found for streptomycin in this series of tests, are the following:

1. The medium used contained no added glucose or salt, both of which decrease the effectiveness of streptomycin in fluid media.¹³



(FIGURES AT TOP OF COLUMNS = % OF TOTAL NUMBER TESTED)

Fig. 1 (Wiggins). Showing the distribution of the minimal inhibitory concentrations (M.I.C.) of three antibiotics for 85 strains of *Pseudomonas aeruginosa*.

every one of the strains was found to be more sensitive to polymyxin B than to either streptomycin or aureomycin. For the five strains tested against circulin as well, the minimal inhibitory concentrations of polymyxin and circulin were always within one tube of each other.

It is evident that polymyxin B was effective over a much narrower range of concentrations (0.08 to 2.5 μg. per cc.) than both streptomycin and aureomycin. The minimal inhibitory concentrations of polymyxin B for this group of organisms is in good agreement with the results reported by other workers.^{9,9,11} For streptomycin, however, the results obtained are somewhat lower than in other

2. The size of the inoculum was relatively small.

Bliss and Todd¹¹ have shown that for *E. coli* decreasing the inoculum size 1,000 times decreased the minimal inhibitory concentration for polymyxin B about eight times, while for streptomycin it was reduced 32 times. Abraham and Duthie¹² found that an increase in inoculum size of 1,000 times raised the inhibitory level of streptomycin for most organisms about four to eight times, but for *Pseudomonas aeruginosa* a similar change in inoculum size raised the inhibitory concentration of streptomycin 30 to 80 times.

It is of interest to note the relationship

between the susceptibility to streptomycin and the year of isolation of the organism. Of 61 strains whose dates of isolation were known, 35 had been isolated after the year 1948 and the remainder prior to that time. Of the "recent" strains more than 50 percent required 40 or more $\mu\text{g. per cc.}$ for inhibition, the lowest minimal inhibitory concentration being 2.5 $\mu\text{g. per cc.}$ of streptomycin. In the older group however, 70 percent had minimal inhibitory concentrations of 2.5 $\mu\text{g.}$ or less and none required more than 10 $\mu\text{g. per cc.}$ for inhibition.

These results are analogous to those reported by Finland and others¹⁶ who said "strains of staphylococci isolated and tested before 1946 were inhibited by significantly lower concentrations of penicillin than those required for strains isolated subsequently."

EFFECTS OF POLYMYXIN B ON CORNEAL EPITHELIUM

METHODS

The effect of local applications of three antibiotics on the cell migration phase of healing in corneal epithelium was tested using male Sherman rats, by the method described by Smelser.¹³

Standard thermal burns of the corneal epithelium were made in both eyes of 100-gm. rats, using a Shahan thermophore with a terminal 1.5-mm. wide, curved to fit the rat's cornea across its width. The tip, heated to 71°C., was applied for five seconds, producing a burn which, if untreated, was almost completely recovered by epithelium at the end of 12 hours.

The solutions to be tested were dropped, at hourly intervals, on the right eyes and the rat held for 15 seconds after each instillation to insure exposure of at least 2.5 minutes duration for 11-hour experiments. The left eyes were untreated controls. At the end of 11 hours, the rats were killed, the eyes were enucleated and fixed overnight in Bouin's solution.

Using a camera lucida with a magnification

of $\times 20$, drawings were made of the outlines of the area on each cornea which had not been recovered by epithelium. The area of each drawing was determined using a planimeter. The average uncovered area for all the treated eyes and the average uncovered area for all the untreated control eyes in each experiment were then calculated. The significance of the difference between these averages was tested, using the t-table of probabilities, and accepting a probability value (P) of 0.02 or less as significant.

Saline solutions of polymyxin B (1.0, 0.1, and 0.01 percent), as well as streptomycin (1.0 percent) and aureomycin (1.0 percent) were tested in this manner.

In addition, the effects on rabbit eyes of local applications of saline solutions of polymyxin B were observed. A central area of corneal epithelium, four mm. in diameter, was marked out with a trephine and abraded with a small curette, in both eyes of eight rabbits. The right eyes of four of these animals were treated for three days by eight hourly instillations (two drops each time) into the conjunctival sac, of 0.25-percent solution of polymyxin. The left eyes were kept as untreated controls.

In the four other rabbits the right eyes were treated with the same solution for the same number of days using five-minute corneal baths twice daily, anesthetizing the corneas with 0.1-percent nupercaine solution before each bath. In the latter group the left eyes were anesthetized in the same way as the right but were untreated otherwise.

The extent of healing was followed using fluorescein to stain unhealed areas. Subconjunctival injections of 0.5 cc. of a 0.25-percent solution in saline were made in the right eyes of four rabbits; the same amount of 0.85-percent saline injected into the left eyes served as controls.

RESULTS

The results of the experiments with the rats are seen in Figure 2 in which the average uncovered area of the treated eyes is ex-

pressed as a percentage of the average uncovered area of the controls, so that 100 percent represents equality or no significant difference. With this method, tested on 17 rats, no difference was obtained when the right eyes were treated with 0.85-percent saline solution.

A 1.0-percent polymyxin-B solution (tested on nine rats) resembled 1.0-percent

no difference could be noted between treated eyes and control eyes. The treated eyes in the corneal-bath group showed somewhat larger areas of staining than those treated by drops when examined after 24 hours, but all the abraded sites failed to stain after 48 hours. By the third day of treatment, no signs of inflammation were observed.

At the conclusion of each corneal bath

TOXIC EFFECT OF POLYMYXIN B, STREPTOMYCIN AND AUREOMYCIN ON HEALING OF RAT'S CORNEAL EPITHELIUM

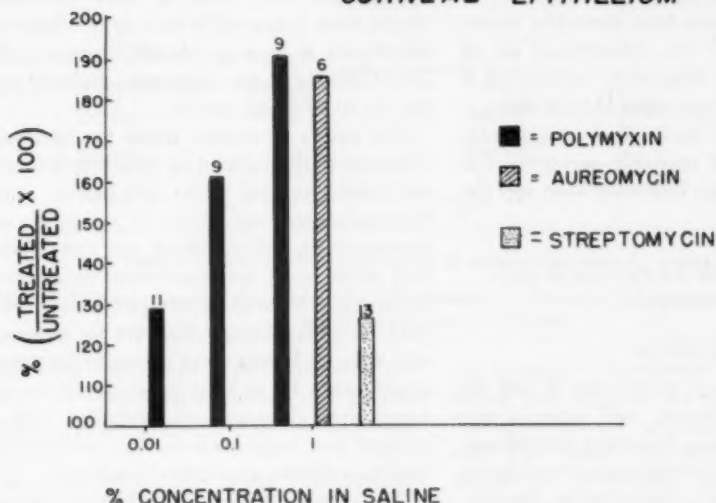


Fig. 2 (Wiggins). The average size of the unhealed burn areas in the treated eyes was divided by the average size of the unhealed burn areas in the control eyes. This figure is given as a percentage and serves as an index of the decreased rate of healing in the treated eyes, with 100 percent representing no significant effect. The figures at the top of each column indicate the number of rats from which the averages were obtained.

aureomycin solution (six rats) with the unhealed areas of the treated eyes exceeding the controls by about 90 percent. A 1.0-percent streptomycin solution (13 rats) produced an effect similar to that of 0.01-percent polymyxin B (11 rats) with the uncovered areas of the treated eyes larger by almost 30 percent.

In the rabbit experiments, when the sizes of the experimental abrasions were compared at intervals after beginning treatment,

a few minute punctate areas of staining could be seen with the corneal microscope, but they were not present 24 hours later.

In the rabbits receiving the subconjunctival injections, both 0.25-percent polymyxin B solution and 0.85-percent saline solution produced a rather milky white bleb. However, within one to two hours the polymyxin-injected eyes showed a profuse purulent discharge accompanied by the signs of acute inflammation of the whole conjunctiva and

slight pericorneal injection but no cells or flare in the aqueous humor.

This reaction subsided within 72 hours, leaving no obvious permanent damage. The control eyes on the other hand showed little or no signs of reaction and appeared normal 24 hours after the injection.

Observations made during the course of treatment of the experimental infections of the cornea in rabbits did not suggest that there was any increase in scar formation or vascularization when 0.1-, 0.25-, or 1.0-percent saline solutions of polymyxin B were used as instillations or corneal baths.

Three patients have been treated by means of instillations into the conjunctival sac of 0.25-percent saline solution of polymyxin B with no discomfort or signs of irritation.

On the basis of these observations polymyxin B seems to resemble aureomycin in its effects on the eye following local application.

PENETRATION OF POLYMYXIN B INTO THE EYE

METHODS AND MATERIALS

The penetration of polymyxin B into the cornea, aqueous humor, and vitreous was studied in rabbit eyes, following instillations, subconjunctival injections, and corneal baths, using a 0.25-percent saline solution. Applications of the drug were made when the corneal epithelium was intact and when a four-mm. central area of epithelium had been abraded.

An agar-diffusion biologic method of assay for polymyxin B was used. It is a well-plate type, using *Brucella bronchiseptica* NRRL B-140 as the test organism.* Twenty-two cc. of Proteose #3 agar (Difco) containing 1.0-percent Tween 80¹⁴ were poured into petri dishes (100 mm. in diameter) and allowed to cool.

The suspension for seeding was prepared

*The test strain was kindly supplied by Dr. Philip G. Stanly of the Chemotherapy Division of American Cyanamid Company.

from a 24-hour growth of the organism on an agar slant by inoculating 150 cc. of nutrient broth with a loop which had been touched to the culture; 2.0 cc. of this broth suspension were flooded onto the test plates and the excess thoroughly drained and withdrawn. The plates were then dried in the incubator for one hour, with the lids off.

Using a six-mm. diameter trephine, plugs of agar were then cut out (five to eight in number) leaving wells, into which 0.03 cc. of the solutions to be assayed were placed, using Kahn pipettes.

For each assay one or more standard curves were prepared by making dilutions of polymyxin B in a glycine-HCl buffer (pH 2.0)¹⁴ usually in two-fold steps from 10 µg. per cc. to 0.039 µg. per cc.

For assays of corneal tissue the standard dilutions were prepared by grinding the cornea from a normal rabbit in a mortar, with Berkshire sand and 5.0 cc. of a solution of polymyxin in buffer (20 µg. per cc.). Two-fold dilutions of the supernatant fluid, after settling was allowed to take place, were then made in buffer. Standard curves for aqueous and vitreous humor were prepared for some experiments by mixing equal quantities of aqueous or vitreous fluid (obtained with a syringe and large-bore needle) and buffer and then diluted as already described.

The samples of vitreous fluid and aqueous humor which were to be assayed were also diluted with equal parts of buffer before being placed in the wells of the test plates. For the cornea, the wet weight of the excised tissue was obtained and it was then ground as for the standards, in 5.0 cc. of buffer solution and the supernatant fluid assayed.

After 0.03 cc. of the unknown samples and the standard solutions had been placed in the wells of the seeded plates, the latter were stored at refrigerator temperature for 20 hours and then incubated at 37°C. for 20 hours. The assays were done in triplicate each time and the average diameters of the zones of inhibition were determined. A standard curve, relating zone diameters to log con-

PENETRATION OF POLYMYXIN INTO RABBIT EYES USING 0.25% SOLUTION IN SALINE. (EXPRESSED IN MICROGRAMS PER CC. OF AQUEOUS HUMOR AND VITREOUS, AND MICROGRAMS PER GRAM OF CORNEAL TISSUE)

	Instillations q 10 min x 6	1 hour after subconj. inj. of 1.25 mgm.	1 hour after 5 min. C. B.
A. Intact corneal epithelium			
Cornea	* < 3.0 (2)	4.5 (4)	< 2.0 (2) 2.2 (2)
Aqueous	< 0.1 (4) 0.3 (4)	0.4 (6)	< 0.1 (4)
Vitreous	< 0.1 (2)	< 0.1 (4)	< 0.1 (4)
B. Area of corneal epithelium 4 mm. in diameter abraded			
Cornea	9.6 (2)	13.2 (6)	30.0 (4)
Aqueous	1.4 (8)	0.8 (6)	4.0 (4)
Vitreous	< 0.1 (2)	< 0.1 (6)	< 0.1 (4)

* Each figure is the average from the number of experiments shown in brackets.

Fig. 3 (Wiggins). Showing the results of the experiments to determine the penetration of polymyxin B, applied locally, into rabbit eyes.

centration per cc. of polymyxin, was prepared for each assay and from this the concentrations of the drug in the samples were read.

By this method the lowest concentration which consistently produced visible zones of inhibition was between 0.03 and 0.05 μ g. per cc. (somewhat more for vitreous). It was not essential for the samples, placed in the wells, to be sterile.

RESULTS

Figure 3 summarizes the results obtained when a 0.25-percent solution of polymyxin B in saline was used, and the determinations were made one hour after the start of treatment. A few experiments with 0.5-percent and 1.0-percent solutions suggest that much higher levels can be obtained when they are used.

Because all the samples were diluted at least 1:2 with buffer before being assayed,

the figures for experiments in which no polymyxin was detected are shown as less than 0.1 μ g. per cc. of aqueous humor and vitreous. The lowest concentration of the drug which could be detected in corneal tissue was somewhat higher because of the dilution factor and varied somewhat depending upon the weight of the cornea.

As might be expected from consideration of the large size of the polymyxin molecule and its relatively low solubility in anything except water and methanol,²⁸ penetration into the eye was low when the corneal epithelium was intact.

The average levels found in the corneal tissue were less than 3.0 μ g. per gm. following instillations, 4.5 μ g. per gm. following subconjunctival injections, and 2.2 μ g. (and less) per gm. following corneal baths. In the aqueous humor, the levels found were, after instillations, 0.3 μ g. per cc. in four eyes and less than 0.1 μ g. per cc. in four other eyes.

Using the corneal baths, the average level was less than 0.1 $\mu\text{g.}$ per cc. of aqueous humor but after subconjunctival injection the average level for six eyes was 0.4 $\mu\text{g.}$ per cc. None was detected in the vitreous humor.

The apparently greater penetration for instillations (less than 3.0 $\mu\text{g.}$ per gm. of corneal tissue) over that found with corneal baths (2.2 $\mu\text{g.}$ and less per gm.) is not necessarily an actual one. It is the result of the variation in lower limits of sensitivity of the assay from day to day and from cornea to cornea because of the dilution factor mentioned above.

Penetration was greater when small defects in the corneal epithelium were present. The highest levels occurred after corneal baths when 30.0 $\mu\text{g.}$ per gm. of corneal tissue and 4.0 $\mu\text{g.}$ per cc. of aqueous humor were found. After instillations and subconjunctival injections 9.6 $\mu\text{g.}$ and 13.2 $\mu\text{g.}$ per gm. of corneal tissue, respectively, were detected. In the aqueous 1.4 $\mu\text{g.}$ per cc. were obtained after instillations and 0.8 $\mu\text{g.}$ per cc. after subconjunctival injection.

The finding in the cornea and aqueous, after subconjunctival injection, of levels higher when the epithelium had been abraded than when it was intact may be related to an increase in the permeability of the stroma and endothelium associated with the trauma of making the abrasions.

IN VITRO SENSITIVITY TESTS WITH COMBINATIONS OF ANTIBIOTICS

There are many reports in the literature which suggest that combinations of some antibiotics, under certain conditions, both in vitro and in vivo, have an antibacterial effect greater than would be expected if the process was simply an additive one.²⁰⁻²³ This phenomenon has been referred to, frequently, as "synergism."

Because the mechanisms by which various antibiotics produce their effects on bacterial cells are not well understood, it is difficult

to assess the results of in vitro tests with combinations of them. However, an attempt was made, by means of sensitivity tests with five different strains of *Pseudomonas aeruginosa*, to determine whether or not there was any evidence of increased antibacterial effectiveness when polymyxin B was combined with each of streptomycin, aureomycin, or circulin.

METHODS AND MATERIALS

The method was essentially the same as that used for the original sensitivity tests. Each antibiotic was tested in duplicate, alone, against each organism. At the same time, 0.4 cc. aliquots of polymyxin B and each one of the other antibiotics were mixed in concentrations from $\times 2$ to $1/128\text{th}$ of the minimal inhibitory concentration found for each drug alone. The inoculum was the same as that used before and the end points were again taken as the absence of visible growth at the end of 20 hours' incubation at 37°C.

RESULTS

Those mixtures, containing less than 50 percent of the minimal inhibitory concentration for each drug alone, which prohibited visible growth, might be considered as suggestive of increased effect. In this category, 11 out of 97 mixtures of polymyxin and streptomycin showed inhibition, 9 out of 103 mixtures of polymyxin and aureomycin and 14 out of 82 with polymyxin and circulin prevented visible growth. Incidence was approximately 12 percent of combinations tested.

The mixtures, containing more than 50 percent of minimal inhibitory concentrations of each drug, which did not prevent visible growth might be suggestive of a decreased effectiveness. In this category combinations of polymyxin B with streptomycin, aureomycin, and circulin, respectively, showed growth in 12 out of 56, 5 out of 9, and 5 out of 75 mixtures. Incidence was also 12 percent of combinations tested.

TABLE 1
RESULTS OF IN VITRO SENSITIVITY TESTS WITH COMBINATIONS OF ANTIBIOTICS
TESTED AGAINST *PSEUDOMONAS AERUGINOSA*

Strain No.		Polymyxin and Streptomycin ($\mu\text{g./cc.}$)		Polymyxin and Aureomycin ($\mu\text{g./cc.}$)		Polymyxin and Circulin (Q-19) ($\mu\text{g./cc.}$)	
3	M.I.C.* of drug tested alone	0.31	160	0.31	10	0.31	0.62
	Inhibition	0.31 plus	2.5	0.15 plus†	1.25	0.31 plus	0.04
	Growth	0.15 plus	2.5	0.15 plus	0.62	0.15 plus‡	0.62
49	M.I.C. of drug tested alone	0.62	2.5	0.62	10	0.62	1.25
	Inhibition	0.62 plus	0.31	0.62 plus	0.08	0.04 plus†	0.62
	Growth	0.15 plus‡	2.5	0.31 plus	2.5	0.31 plus	0.31
57	M.I.C. of drug tested alone	0.62	2.5	0.62	2.5	0.62	1.25
	Inhibition	0.15 plus†	0.62	0.31 plus†	0.15	0.31 plus†	0.04
	Growth	0.08 plus‡	2.5	0.08 plus‡	2.5	0.15 plus	0.62
71	M.I.C. of drug tested alone	1.25	20	1.25	10	1.25	1.25
	Inhibition	0.31 plus†	10	0.62 plus†	0.31	0.31 plus†	0.15
	Growth	0.15 plus	10	0.15 plus‡	10	0.15 plus	0.31
72	M.I.C. of drug tested alone	1.25	2.5	1.25	10	1.25	1.25
	Inhibition	0.62 plus†	0.31	0.62 plus	5	0.62 plus†	0.08
	Growth	0.15 plus‡	2.5	0.62 plus	2.5	0.31 plus	0.62

* Showing the minimal inhibitory concentrations (M.I.C.) for each drug when tested alone, as well as the lowest concentrations which, when mixed, prevented visible growth, and the highest concentrations which, when mixed, failed to prevent visible growth. Readings were made after 20 hours' incubation at 37° C.

† Mixtures containing less than 50% of the M.I.C. of each drug.

‡ Mixtures containing more than 50% of the M.I.C. of each drug.

Table 1 shows the lowest combined concentrations producing inhibition and the highest combined concentrations in which growth occurred for each of the five strains tested. The minimal inhibitory concentrations of each drug alone are also shown. It is evident that, under the conditions of these tests, even where an increase or decrease in effectiveness with mixtures might be suspected, this certainly is not striking.

In only two mixtures was the minimal inhibitory concentration of polymyxin or the drug tested with it reduced to less than one half of the concentrations required when they were tested alone. Similarly, no mixture which contained the equivalent of the

minimal inhibitory concentration (when tested alone) of one drug plus more than one-half the minimal inhibitory concentration (tested alone) of the other failed to inhibit growth.

The results of this rather crude method of testing combinations of antibiotic indicate that there is no marked increase or decrease in the antibiotic activity when polymyxin B is combined with aureomycin, streptomycin, or circulin in vitro. This is in agreement with the report of Pulaski and others¹⁷ for streptomycin and aureomycin combined with polymyxin. A more sensitive test which measures the effects of antibiotics on the growth curves of organisms might give more information.

TREATMENT OF EXPERIMENTAL PYOCYANEUS
INFECTION IN RABBITS' CORNEAS

EXPERIMENTAL INFECTIONS

The corneas of both eyes of each rabbit were prepared before inoculation by marking out with a trephine a central area four-mm. in diameter and abrading the epithelium within it by means of a small curette.

At first the corneas were inoculated from a 24-hour broth culture of the organism by rubbing the abrasions for one minute with a loopful or with a cotton-tipped applicator which had been dipped in the culture. With this method a large number (11 out of 22) of rabbits did not develop progressive infec-

tion in the control eyes and so had to be discarded. For this reason the remainder (34 rabbits) of the experimental infections were produced by rubbing the abrasions for one minute with a cotton-tipped applicator which had been dipped in a very heavy saline suspension of the organism.

There is considerable variation in virulence of different strains of *Pseudomonas aeruginosa* and the experimental infections which occurred have been classified into two groups according to the severity of the lesions in the control eyes.

In one group are the so-called "mild" infections which followed inoculation from the 24-hour broth cultures of strains A and D

TABLE 2
RESULTS OF TREATMENT OF EXPERIMENTAL PYOCYANEUS INFECTIONS:
A. "MILD" TYPE OF INFECTION

Hours after Inoculation	Treatment					Results	
	Drug and % Solution Used	Method of Treatment	Days of Treatment	Strain No. & in Vitro M.I.C.*	Number of Rabbits	Treated Eye	Control Eye
6	Polymyxin 1.0%	Corneal bath	2	A 0.62 D 2.5	2	0 0	xx xxxx
18	Polymyxin 0.1%	Drops	1	A 0.62	2	0 0	xx xx
24	Polymyxin 1.0%	Corneal bath	5	D 2.5	4	x x x x	xxx xxx xxx perfor.
	Polymyxin 1.0%	Drops	1	D 2.5	3	0 0 0	x x x
	Polymyxin 0.25%	Corneal bath	3	59 0.3	3	x x xx	xxx xxx xxx
	Streptomycin 1%	Corneal bath	3	59 > 160	3	xxxx xx xxx	xxxx xx xxx
	Circulin 0.25%	Corneal bath	3	59 ?	3	x x x	xxxx xxx xxx

* M.I.C. in micrograms per cc.

0—No progression; healed without scarring.

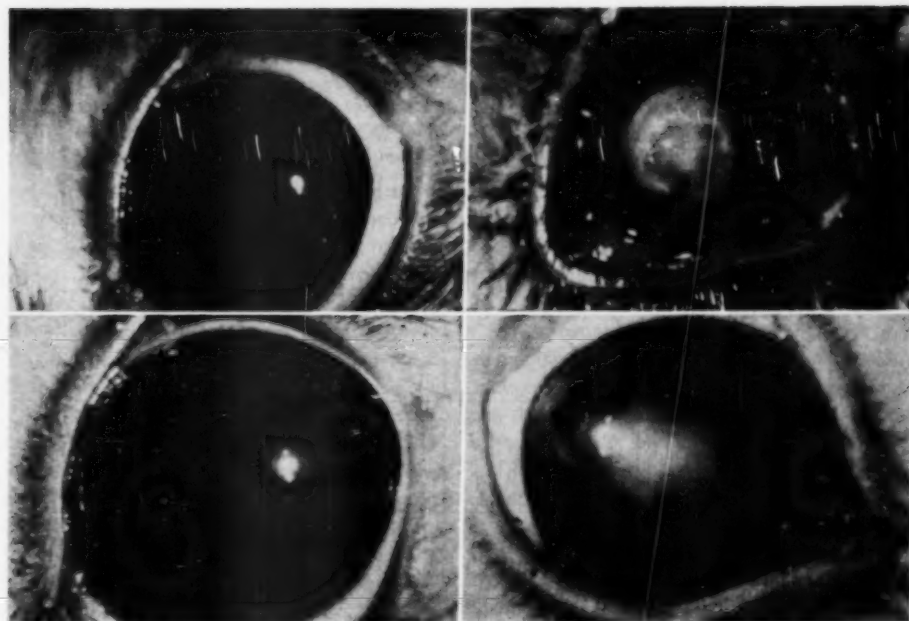
x—Central infiltration; healed with faint scar.

xx—Dense central infiltration; healed with dense central scar.

xxx—More than one half cornea infiltrated; healed with dense scar.

xxxx—Whole cornea infiltrated; healed with complete vascularized scar.

Perfor.—cornea ruptured.



Treated

Untreated

Fig. 4 (Wiggins). Showing treated and control eyes of a rabbit with the "mild" type of infection on the third day and one month after inoculation. The right eye was treated by six hourly instillations into the conjunctival sac for one day, of 0.1-percent polymyxin B, starting 18 hours after inoculation. (Top) Third day—untreated eye shows infiltration of the center of the cornea. Treated eye appears normal. (Bottom) One month—control eye shows central scar.

and from the heavy suspension of strain 59. The control eyes of these rabbits characteristically showed, within 48 hours after inoculation, dense central infiltration of the cornea accompanied by the signs of acute inflammation and profuse discharge from the conjunctival sac. Within the next two to three days, however, recovery would begin and, by the end of two to three weeks, healing had taken place, leaving a central corneal scar which varied from a faint opacity to a dense vascularized leukoma (fig. 4).

The second group, or so-called "severe" infections, followed inoculation from heavy suspensions of strains C and 57. Characteristically the control eyes, in this group showed, within 18 hours after inoculation, dense central infiltration of the site of the abrasion, frequently extending beyond its

limits. There was also profuse purulent conjunctival discharge and signs of acute inflammation.

Within 48 hours, the whole cornea was completely infiltrated, and by the end of one week after inoculation the corneas of all but three animals had perforated. In Figure 5, the control eye shows the appearance at various stages in the course of a "severe" infection.

TREATMENT

Treatment was either by means of five-minute corneal baths, twice daily, or by six to eight hourly instillations into the conjunctival sac of saline solutions of the drug, each day for periods of one to eight days.

Solutions of polymyxin B were used in strengths of 0.1, 0.25, and 1.0 percent and

TABLE 3
RESULTS OF TREATMENT OF EXPERIMENTAL PYOCYANEUS INFECTIONS:
B. "SEVERE" TYPE OF INFECTION

Hours after Inoculation	Treatment					Results	
	Drugs and % Solution Used	Method of Treatment	Days of Treatment	Strain No. & in Vitro M.I.C.*	Number of Rabbits	Treated Eye	Control Eye
6	Polymyxin 1.0%	Corneal bath	2	C 2.5	2	0 0	xxx perfor.
18	Polymyxin 0.1%	Drops	8	C 2.5	3	xxx xxx xxx	perfor. perfor. perfor.
	Polymyxin 1.0%	Corneal bath	8	C 2.5	2	xx xx	perfor. perfor.
	Polymyxin 0.25% plus Streptomycin 0.5%	Corneal bath	3½	57 0.62 2.5	3	x xx xx	perfor. perfor. perfor.
	Polymyxin 0.25%	Corneal bath	3½	57 0.62	3	x x x	perfor. perfor. perfor.
24	Polymyxin 0.1%	Drops	5	C 2.5	3	xxxx xxxx xxxx	perfor. perfor. perfor.
	Polymyxin 0.25%	Corneal bath	2½	57 0.62	3	xx xx xxxx	perfor. xxxx xxxx
	Circulin 0.25%	Corneal bath	2½	57 1.25	3	xxx xxx xx	perfor. perfor. perfor.
	Streptomycin 1.0%	Corneal bath	2½	57 2.5	3	xxx xxx perfor.	perfor. perfor. perfor.

* See Table 2.

Abbreviations: same as in Table 2.

treatment was started at intervals of 6, 18, and 24 hours after inoculation. When the experimental lesions appeared to be the same in both eyes, the right eye was treated and the left kept as a control. When one eye appeared to be more severely infected it was selected as the eye to be treated, and the other eye kept as untreated control.

RESULTS

The appearance of the eyes was recorded daily in notes and at frequent intervals by kodachrome photographs. On the basis of these the course of the infection in each eye

has been classified according to the most severe stage of infiltration seen grossly and the extent of the damage after the acute process had subsided and healing had taken place. Tables 2 and 3 summarize the results of treatment in the two groups.

In 11 rabbits with the "mild" type of infection, treatment with 0.1 and 1.0-percent polymyxin B, started at 6, 18, and 24 hours after inoculation, prevented progression of the infection in all of them, whether the infecting organism was relatively resistant (minimal inhibitory concentration of polymyxin—2.5 µg. per cc.) or relatively

susceptible (minimal inhibitory concentration—0.62 $\mu\text{g. per cc.}$). An example of this group is seen in Figure 4.

Nine rabbits were inoculated with a strain which was resistant *in vitro* to streptomycin (minimal inhibitory concentration more than 160 $\mu\text{g. per cc.}$) but relatively sensitive to polymyxin (minimal inhibitory concentration 0.3 $\mu\text{g. per cc.}$). Three were treated with 0.25-percent polymyxin, three with 0.25-percent circulin, and three with 1.0-percent streptomycin, by means of corneal baths, starting the treatment 24 hours after inoculation and continuing for three days.

Those treated with streptomycin showed no evidence of beneficial effect, the lesions in the treated eyes following the same course as the controls. Both circulin and polymyxin, however, prevented further extension of the lesions while the control eyes progressed to the stage of complete corneal infiltration but did not perforate.

In the 19 animals with "severe" infections which were treated with polymyxin B all but three of the control eyes, but none of the treated eyes, perforated. Two animals infected with a relatively resistant strain (minimal inhibitory concentration polymyxin *in vitro*—2.5 $\mu\text{g. per cc.}$) and treated with 1.0 percent polymyxin B, beginning six hours after inoculation, failed to develop progressive infection and the abrasions healed without gross scarring.

When treatment of this "severe" type of infection was delayed until 18 hours after inoculation, both eyes characteristically showed infiltration of the central area of the cornea, which frequently extended beyond the limits of the original abrasion and was accompanied by a profuse conjunctival discharge.

Three rabbits in this group, infected with the relatively resistant strain and treated with 0.1-percent polymyxin-B solution, showed progression of the lesions in both eyes, but only the untreated eyes perforated. In two rabbits infected with the same organism and treated with 1.0-percent solution of

polymyxin there was no extension of the lesions in the treated eyes although the controls again perforated.

In six animals infected with a more sensitive strain (minimal inhibitory concentration polymyxin—0.62 $\mu\text{g. per cc.}$) treatment was started when the lesions had reached the 18-hour stage, using 0.25-percent solution for three of them and the same solution, containing in addition 0.5-percent streptomycin, in the other three.

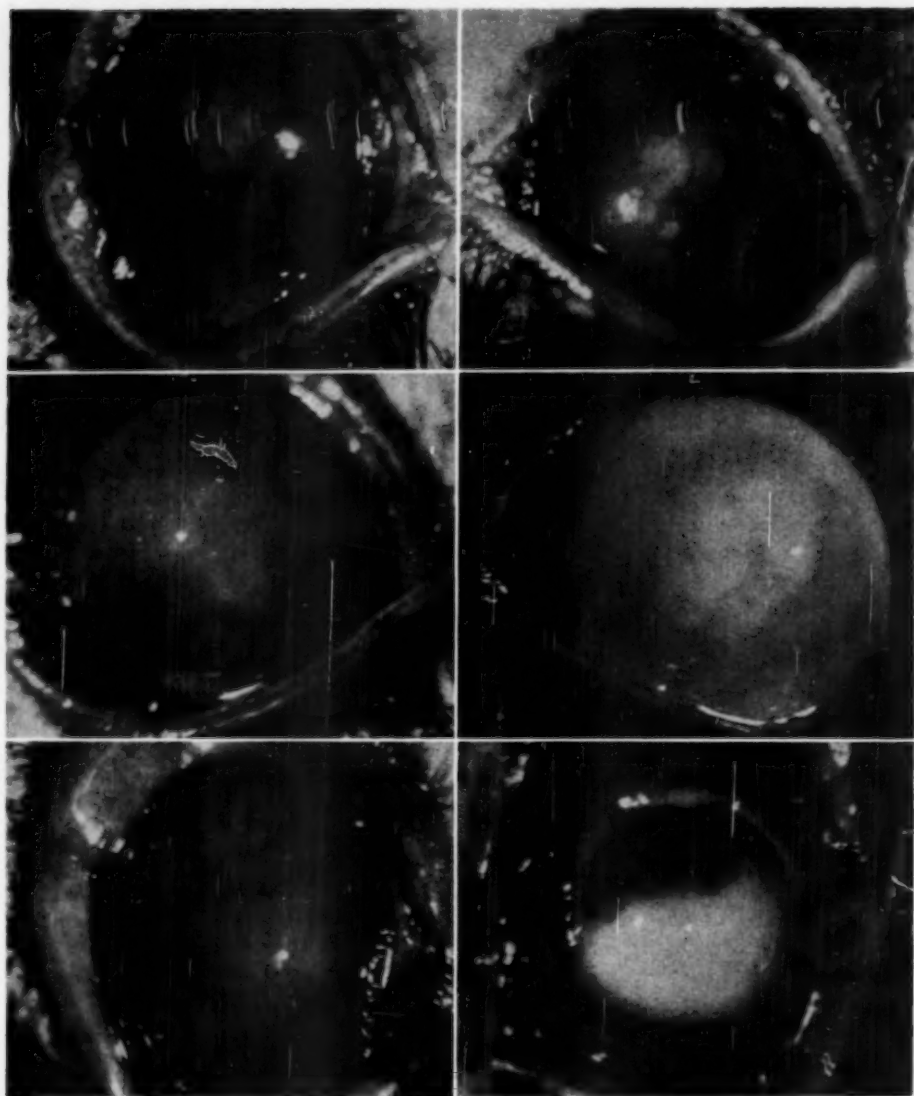
Both forms of treatment prevented further extension of the infection although the controls perforated (fig. 5). There was no striking difference in the results with polymyxin alone or combined with streptomycin.

In the "severe" infections, by the end of 24 hours after inoculation there was dense infiltration of the central part of the cornea extending well beyond the limits of the original abrasion. When treatment was delayed until this stage had been reached, the beneficial effects were not so strikingly evident.

Three animals infected with the relatively resistant strain were treated with 0.1-percent solutions of polymyxin and, in these, the treated eyes continued to show progression of the lesions, but although all the control eyes perforated none of the treated eyes did.

Nine rabbits were infected with a strain which was relatively sensitive *in vitro* to both circulin (minimal inhibitory concentration—1.25 $\mu\text{g.}$) and polymyxin (minimal inhibitory concentration—0.62 $\mu\text{g.}$) and quite sensitive to streptomycin (minimal inhibitory concentration—2.5 $\mu\text{g.}$). Twenty-four hours after inoculation, treatment by means of corneal baths was started, using 0.25-percent polymyxin solution for three animals, 0.25-percent circulin for three others, and 1.0-percent solution of streptomycin for the remaining three.

There was no marked difference in the results for the three groups and each drug showed some beneficial effect. Only one treated eye perforated and this was in one of the streptomycin-treated rabbits.



Treated

Untreated

Fig. 5 (Wiggins). Showing treated and control eyes with the "severe" type of corneal infection. Treatment was with 0.25-percent polymyxin B administered as a corneal bath (five minutes), twice daily for three days, beginning 18 hours after inoculation. (Top) 18 hours after inoculation (before treatment). Shows central infiltration of both corneas. (Middle) 48 hours after inoculation. The untreated cornea is completely infiltrated while the infiltration of the treated cornea has not spread appreciably. (Bottom) 15 days after inoculation. The untreated cornea ruptured on the seventh day. The treated cornea shows dense central scarring which later diminished in size and density to a faint central opacity.

Too few experiments have been done so far to compare the effectiveness of treatment by corneal baths with that by hourly instillations into the conjunctival sac.

DISCUSSION

A rather extensive literature on the subject of treatment of pyocyanus infections of the cornea includes few reports of success until the year 1940. At this time Joy²⁶ reported beneficial effects in experimental infections of the rabbit cornea when large doses of sulfapyridine were given orally, either before or within six hours after infection.

Robson and Scott^{27, 28} reported good results in experimental infections with instillations of 30-percent solutions of sodium sulfacetamide given four or five times daily, if the treatment was begun six hours after inoculations.

Somewhat better results were obtained by von Sallmann²⁹ in experimental lesions treated with sulfadiazine locally by iontophoresis and combined oral administration, when treatment was started 18 hours after inoculation. He mentions success with this combined therapy in two patients.

Bellows and others³⁰ reported that three instillations of 1.0-percent solution of streptomycin, at two-hour intervals, prevented the development of pyocyanus ulcers in rabbits, when started within six hours of the time of inoculation. According to the same worker³¹ aureomycin as a 1.0-percent solution was less effective than streptomycin, preventing experimental corneal ulcers in one out of five animals when treatment started six hours after inoculation.

The results of in vitro sensitivity tests in this study are in agreement with the reports of others that polymyxin B is a more effective antibiotic against *Pseudomonas aeruginosa* than aureomycin or streptomycin and is similar to circulin. This was evident for strains isolated in widely separated geographic areas, both stock and recent.

Polymyxin B has been shown by others

to be primarily bactericidal, with a rapidly lethal action and against which it is difficult to produce resistant strains.¹⁸ It is stable in saline solution for relatively long periods of time.

In the experiments reported here, polymyxin B, applied locally, penetrated the rabbit eye when there were defects in the epithelial layer. Topical applications did delay the migration of corneal epithelium in rats to about the same degree as aureomycin; however, they did not delay the healing of epithelial abrasions in the rabbit's cornea and were well tolerated by the human eye when a 0.25-percent solution in saline was used.

When polymyxin B was used locally in the treatment of severe infections by *Pseudomonas aeruginosa* of the rabbit cornea, beneficial effects on the course of the lesions were observed when treatment (with 0.25-percent solution) was started as late as 24 hours after inoculation, at a time when the infections were well advanced.

On the basis of the findings just mentioned, polymyxin B would seem to merit clinical trial in *Pseudomonas aeruginosa* infections of the cornea in humans. In addition it might be helpful in the treatment of surface infections of the eye, due to Gram-negative organisms (except the genus *Proteus*) which do not respond to other forms of treatment.

SUMMARY

1. Polymyxin B, on the basis of weight, was more effective than either aureomycin or streptomycin when tested in vitro against 85 widely selected strains of *Pseudomonas aeruginosa*. It was effective over a much narrower range of concentrations than the other two substances.

2. The toxic effects of topical applications of polymyxin B on corneal epithelium were similar to those of aureomycin, both being more toxic than streptomycin. Local applications of 0.25-percent solution of polymyxin B in saline did not delay the healing of abra-

sions of corneal epithelium in rabbit eyes and were well tolerated in human eyes.

3. Penetration into rabbit eyes after local administration of polymyxin B was low when the epithelial layer was intact but higher when there were small defects in the epithelium.

4. Beneficial effects were noted during the treatment with polymyxin B of severe experimental pyocyanus infections of the cornea when it was started as late as 24 hours after inoculation, by which time the lesions were quite well advanced.

5. No striking evidence of increased or decreased antibacterial effect was observed when sensitivities of five strains of *Pseudomonas aeruginosa* were tested in vitro

with combinations of polymyxin B and streptomycin, aureomycin, or circulin.

6. Circulin (Q-19) resembled polymyxin B in its antibiotic activity for five strains of *Pseudomonas aeruginosa* tested in vitro, and for two strains, tested in vivo.

7. The suggestion was made that polymyxin B be given a trial in treatment of *Pseudomonas aeruginosa* infections of the cornea in humans.

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ACKNOWLEDGMENT.

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DISCUSSION

DR. HENRY F. ALLEN (Boston): It is a privilege to discuss such stimulating papers as those of Dr. Ross and Dr. Wiggins, as well as the preceding one by Dr. Halbert. It is certainly on the basis of such fundamental studies as these that a rational basis of therapy can be derived.

During the past six months we have seen four cases of pyocyanus keratitis at the Massachusetts Eye and Ear Infirmary, all from the same source. I have seen these in consultation with the ophthalmologist of a large industrial plant in the vicinity of Boston. The first case occurred last December, the second one in March, and the last two within recent weeks.

A note about the epidemiology of these four cases is in order. They all followed removal of imbedded corneal foreign bodies at the plant dispensary, which handles between 10 and 15 such injuries a day. The routine of treatment was anesthesia with tetracaine and irrigation, following removal, with a proprietary sulfonamide drug.

It is of some interest that the eyes were not patched following the removal of the foreign body but that the patients were brought back for drops every two hours so that they could remain upon the job. That is of special interest in view of the conclusions of McCulloch, reported in the *Archives of Ophthalmology* in 1943, who found that he could produce pyocyanus keratitis in rabbits only when he patched the eyes following trauma of the cornea and installation of pyocyanus cultures.

The bacteriologic survey of the plant dispensary

revealed that all instruments and solutions were culturally sterile except the proprietary sulfonamide solution which was used to irrigate these particular eyes following removal of the foreign bodies. That gave a positive culture for pyocyanus, both from the dispensing bottle and from stock solutions of the same drug.

The treatment of these cases does not bring us to any particular conclusions but I will go through it briefly in order that you may form some impression of what was done. If I may have the lights off, I will show some slides of the first case from which the pyocyanus organisms were recovered immediately on the first culture.

(Slide). This patient was placed on polymyxin, 1.0 mg. per cc. in the form of local drops every hour, and was kept on that for 10 days. The first picture shows a somewhat superficial type of infection by comparison with the ones which we saw subsequently.

(Slide). Here you will see the same eye at the end of 10 days, with a rather definite residual corneal opacity and central staining area. The eye appears white because cortisone was used locally in an effort to improve epithelial regeneration. Finally, all treatment was stopped and the eye healed with a residual opacity such as you see.

The second eye was not seen in consultation and was treated with chloromycetin. That, too, was a superficial infection and sensitivity studies were not done on that strain.

In the case of the third and fourth eyes which

came in during the past weeks and which led to the epidemiologic survey of the dispensary, material obtained from the cornea in the former did not result in a positive culture on two attempts. Only when the cornea had gone on to complete abscess formation and, as a last resort, paracentesis was done, was pyocyanus obtained. By that time, the eye was ready for evisceration, but that strain of organism was found to be sensitive to 0.5 µg. per cc. of polymyxin.

The last patient entered the hospital within a day of the evisceration of the eye which I have just described, and a direct smear of the cornea showed Gram-negative rods which were confirmed on culture to be pyocyanus.

That patient was immediately started on polymyxin, 1.0 mg. per cc., with drops every hour, and also was given terramycin orally, a gm. a day. The organism was sensitive to 0.5 µg. of polymyxin and resistant to terramycin. The original lesion was dead center in the cornea with a concentric ring abscess below Bowman's membrane, and on the next day a third concentric zone of edema was visible in the peripheral part of the stroma.

Under treatment the hypopyon receded and the lesion seemed to "harden" out. The patient was kept on this regimen for 10 days, at the end of which time the staining had ceased and cultures had become negative.

The patient then eloped from the hospital—because of extreme nervousness he refused to stay any longer—and he was followed in the office of the consulting ophthalmologist on a daily basis. He returned three days ago with a staining cornea, a large hypopyon, and a positive culture for pyocyanus. He has been readmitted to the hospital.

The chief conclusion to be drawn from these rather random observations is that pyocyanus is often brought to the eye as the result of treatment rather than as the result of accident. Its role as a contaminant of fluorescein, eserine salicylate, and neosilvol solutions is well known. The present instance is to my knowledge the first in which a sulfonamide stock solution was contaminated with pyocyanus.

DR. ALSON E. BRALEY: (Iowa City): I am sorry Dr. Douvas isn't here to present the data that we have on pyocyanus in a comparatively small group of antibiotics. We have recently seen five cases of rather severe burns with pyocyanus contaminations of the skin that extended to the eye. Some of these organisms have been shown, by sensitivity tests, to be most susceptible to gantrisin, a highly soluble chemotherapeutic agent

which can be used clinically. Most of the strains of pyocyanus that we have had at Iowa City recently have not been particularly susceptible to polymyxin but have been more susceptible to chloromycetin.

I think we should congratulate Dr. Ross, who is in a small town and has done what I believe to be a very severe test of the type of treatment that he had to undertake. With as severe an infection as he had, you would expect him not to get as good results as Dr. Wiggins got. It was to a very severe test that he put his polymyxin.

There is no doubt that certain strains of pyocyanus show susceptibility to polymyxin. I have been using polymyxin for about two or three years, since a short time after it came out, and I felt at first that it was the most effective of the antibiotic agents against the pyocyanus. The fact that it does not penetrate the cornea readily also points to the fact that you could not expect to get any effect on a very severe, deep infection by using the polymyxin locally in the form of drops. The corneal bath would give a higher concentration than merely the drops. Iontophoresis might increase the concentration. I have not seen any figures on the use of iontophoresis with polymyxin.

I think both Dr. Ross and Dr. Wiggins should be congratulated on their work, first to show that, in a severe and deep infection, none of the antibiotics, probably, are effective, and certainly polymyxin is not. Polymyxin in some strains of pyocyanus may be effective in local therapy.

DR. LUDWIG VON SALLMANN (New York): I am sure that Dr. Wiggins is going to answer the questions which have been raised and will be able to explain the differences in the results reported by Dr. Ross and by him, but I would like to say, with respect to the discussion of Dr. Braley, that he based his conclusions on instillations of solutions of polymyxin D in a concentration of probably not more than 0.1 percent, whereas, instillations of 0.25 percent and even 0.5 percent were tolerated well by the few patients which had been treated successfully in the Eye Institute during the last year.

The corneal baths will reach infections which are deep-seated in the posterior portion of the cornea.

I do not think one can say that only a few strains of *Pseudomonas aeruginosa* are susceptible to this antibiotic and other strains not when all of the 86 strains collected by Dr. Wiggins from various parts of North America and of Europe were found to be highly susceptible to polymyxin B.

THE EFFECT OF ACTH ON EXPERIMENTAL EXOPHTHALMOS*

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For a number of years many investigators have been interested in exophthalmos as it is related to the anterior pituitary and the thyroid gland. At the present time there can be little doubt that the pituitary is related to Graves' disease in general and to the ophthalmopathy in particular. How still remains a mystery. This mechanism by which anterior pituitary substance, or substances, produces thyroid hyperplasia or ocular protrusion has not as yet been found.

Schockaert,¹ however, first produced a thyroid hyperplasia and exophthalmos in young ducks with anterior-pituitary extracts. Smelser,² using a thyrotropic anterior-pituitary extract, produced an exophthalmos in the thyroidectomized guinea pig which was due to an actual increase in the orbital contents. Pochin³ reported the same findings, using dried pig anterior-pituitary extract, except the exophthalmos occurred in the unthyroidectomized as well as in the thyroidectomized guinea pig.

Dobyns,⁴ using several methods of measuring the intercorneal distance of the guinea pig, reported exophthalmos in the thyroidectomized guinea pig without the use of any pituitary substance. Furthermore, he showed that crude anterior-pituitary extract will increase considerably the exophthalmos of the thyroidectomized guinea pig; as will also a thyrotropic hormone labeled Antuitrin T which seems to be most rich in the exophthalmic factor. However, a third substance "purified" thyrotropic factor had little if any effect in producing an ocular protrusion.

Dobyns,⁵ in seeking a substance which would produce exophthalmos but not thyroid hyperplasia, administered a preparation separated from the thyrotropic fraction called the

specific metabolic principle.⁶ This preparation did raise the metabolic rate within several hours without thyroid hyperplasia but was unsuccessful in producing an exophthalmos.

Jefferies,⁷ using iodinated pituitary extract which inactivated 95 percent of the thyrotropic principle, was able to show that sufficient exophthalmos and fat-mobilizing activity remained to produce a demonstrable effect on young guinea pigs. He concluded that the role of thyrotropic hormone in experimental exophthalmos following pituitary injections is at best an auxiliary one and the primary factor for this phenomenon remains unidentified.

Jefferies⁸ next injected guinea pigs with ACTH for three days taking daily exophthalmic measurements. He found no change in the intercorneal distance.

At the present time, therefore, experimental evidence suggests that the thyrotropic principle and exophthalmic principle are not identical. This would seem true if a reason is sought to explain the exophthalmic and thyrotropic effect of crude anterior pituitary and Antuitrin T in contrast to only the thyrotropic effect of the "purified" thyrotropic hormone. Perhaps, in the process of purification of the thyrotropic hormone, an exophthalmos-producing substance has been lost.

Previous investigators have pointed out the edema of the orbital tissues of the guinea pig made exophthalmic with the use of pituitary extract. It seemed possible that the effect of ACTH, which is a product of the anterior pituitary, on the adrenal cortex of the animal might be responsible in some degree for orbital edema reported in the exophthalmic animals previously.

It was also after noting a case of malignant exophthalmos treated at the Buffalo General Hospital with ACTH that the present study was started to determine the rela-

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Fig. 1 (Dayton). Appearance of patient on admission to hospital and before ACTH therapy was begun.

tionship if any between ACTH and the thyrotropic hormone.

CASE REPORT

This was the case of a 38-year-old white woman who entered the hospital with a marked exophthalmos and ptosis of the right lid (fig. 1). This followed a thyroidectomy eight months previously. Her ocular changes had begun two months after surgery. Before admission to the hospital, she had had X-ray therapy to her pituitary totaling 2,000 roentgen units in the hope of arresting the process.

In the hospital, she was placed on ACTH, receiving 80 mg. per day for six days, a total dose of 480 mg. Little change in her ocular status took place over the six-day



Fig. 2 (Dayton). Appearance of patient four days before death.

period of ACTH therapy. However, the day following discontinuance of ACTH her ocular status overnight became critical.

There was a marked increase in the exophthalmos which was accompanied by pain across the bridge of the nose and forehead. The orbital swelling was great enough to mask completely the ptosis on the right. She was operated that afternoon. A Naffziger type of decompression of both orbits was done by the neurosurgery department.

Despite decompression, the exophthalmos persisted and the corneas of both eyes became ulcerated (fig. 2). Ten days later the lids were sutured together. The patient progressed steadily downhill. Shortly before death, she was in severe shock with periods of deep cyanosis followed by generalized convulsive seizures. Electrocardiograms showed complete heart block. The patient died two days after suturing her lids.

The pathologic diagnosis was a diffuse myocarditis involving both ventricles with distinct dilatation, especially of the right heart (fig. 3). Histologic study showed a severe subacute myocarditis. There were focal and confluent diffuse areas of muscle degeneration and necrosis. The inflammatory infiltration included many eosinophils, lymphocytes, and macrophages. The skeletal musculature was studied in 12 different areas. All but one showed the same histologic picture. The process other than in the heart was most severe in the extraocular muscles (fig. 4).

METHOD

The anterior-pituitary product used in this study was the "purified" thyrotropic hormone prepared for clinical investigation by Armour and Company;¹ and a crude pituitary preparation prepared for investigation by Parke-Davis and Company. The ACTH used was that in general use at the Buffalo General Hospital.

Thirty-two guinea pigs were utilized. There was an equal distribution between males and females. The animals were on a

standard guinea-pig diet of purina guinea pig pellets, lettuce, and hay. Their weights were determined every other day and initially they weighed between 200 and 400 gm.

The intercorneal distance was recorded three times daily and forms the basis for this report. Some mention should be given as to the method of measurement of the intercorneal distance of the guinea pig, particularly since the variations of tenths of millimeters has been considered as quite important in other reports.

We first used a method suggested by earlier reports but in our hands it was found inaccurate.⁴ With this instrument, binocular vision was impossible, and a large amount of parallax was encountered.

It was felt that the simple method used by Pochin of aligning the blades of the calipers with the apices of the cornea, holding the calipers just above the cornea, is more accurate, easily accomplished, and demands the minimum of effort. A third method was devised which consisted of a lens with the image of the animal's head brought to a focus on a ground-glass screen. A pair of hairlines with a Vernier calipers were built into the instrument (fig. 5).

With this instrument, however, the eyes of the animal had to be in exact focus which necessitated the construction of a platform (not shown) with a cradle for the head of the animal with the eyes set at the exact focal distance. In this experiment we noted that a normal variation of the intercorneal distance up to 0.5 mm. occurred in a series of determinations.

It is necessary to obtain repeated measurements of the intercorneal distance for significant findings. The guinea pig possesses considerable smooth muscle within the orbit and has the ability to retract the eyeball up to 0.5 mm. Furthermore, variations of a few tenths of a millimeter occurred with the activity of the animal and also with the time of feeding.

Nevertheless, we do feel, as do other investigators, that with successive measurements

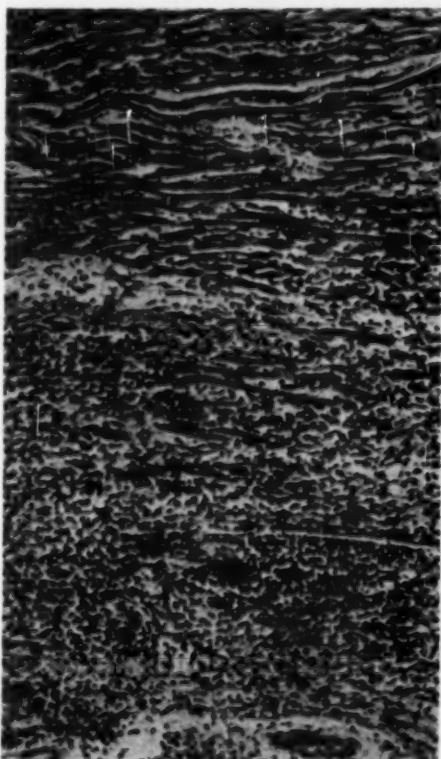


Fig. 3 (Dayton). Photomicrograph of cardiac muscle, showing severe muscle necrosis with predominate infiltration of eosinophils.

it is possible to determine the ocular status within a few tenths of a millimeter for a given day. No one method of measurement or combination will give the same reading of the intercorneal distance to tenths of a millimeter without some difference because of the reasons just mentioned.

The procedure of thyroidectomizing the guinea pig is simple and, by virtue of the small anatomy, is suited particularly to the talents of the ophthalmologist. However, we encountered complications following surgery which led to a high mortality.

One complication was the severance of the recurrent laryngeal nerves which is difficult to avoid. Another was postoperative pneumonia due to aspiration. In the series

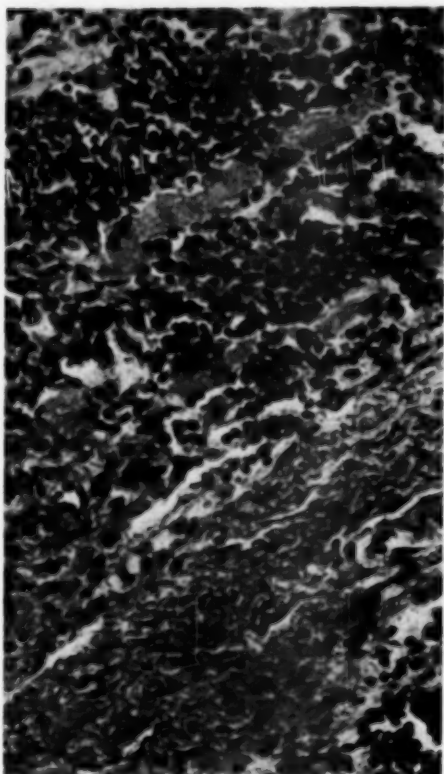


Fig. 4 (Dayton). Photomicrograph of extraocular muscle, showing degenerative changes.

of six thyroidectomized animals, only two were considered to be sufficiently recovered for valid conclusions as to ACTH therapy.

All of the thyroids removed were identified by histologic section. An attempt was made to perform a total thyroidectomy on every animal but undoubtedly small bits of the thyroid tissue remained.

FINDINGS

In the first series, the purified thyrotropic hormone from Armour's* was investigated; 24 guinea pigs were used—six were thyroidectomized and treated, 12 were intact and treated, and six served as controls.

The treated animals received a 3.0 mg. dose of the thyrotropic hormone per day for a period of three days and then a daily dose of 5.0 mg. for 13 days more. On the 10th day, seven of the animals, including one thyroidectomized, also received ACTH therapy. The ACTH administered amounted to a total dose of 3.0 to 4.0 mg. per day which was ample considering the size of the animal. The remaining treated animals continued with the daily injection of the purified thyrotropic hormone.

After ten days of administration of purified thyrotropic hormone to 12 intact guinea pigs, no significant increase in the intercorneal distance was noted. On the 10th day, to half or six of this group of animals, ACTH was administered along with the purified thyrotropic hormone. We still failed

* Assayed and found to contain three to five Junkmann-Schoeller units per mg.



Fig. 5 (Dayton). Instrument used to measure intercorneal distance.

to note any change in the intercorneal distance.

Only two (fig. 6) of the six thyroidectomized animals were considered as recovered sufficiently for any conclusions. One of the animals did develop an exophthalmos which amounted to an increase of 1.8 mm. As pointed out previously, the thyroidectomized animal develops some degree of exophthalmos spontaneously.

However, this increase occurred rather too rapidly after the administration of the purified thyrotropic hormone to be explained only on this basis. This animal also received ACTH on the 10th day of thyrotropic hormone treatment but little change occurred in the intercorneal distance, and a plateau seemed to be reached which was not influenced by the introduction of ACTH.

The other thyroidectomized animal which received the purified thyrotropic hormone but not the ACTH developed an exophthalmos with an 0.8-mm. increase in the intercorneal distance. This could be due to the thyroidectomy and is more in keeping with the usual curve found in an operated animal.

In the second series the crude anterior-pituitary hormone from Parke-Davis was studied in its relationship to ACTH. Eight intact guinea pigs were utilized—six were treated and two served as controls.

The six treated animals received a daily



Fig. 6 (Dayton). View of exophthalmic pig (right) with control (left).

dose of extract equivalent to 25 Junkmann-Schoeller units of thyrotropic hormone. All developed a measurable exophthalmos between one and two mm. within four days. Three of these animals also received a daily injection of 4.0 mg. of ACTH. No significant difference in the intercorneal distance was noted in these two groups. The animals were killed on the 10th day. The pathologic changes in the orbit in both groups were consistent with those reported by other investigators.^{8,9}

Smelser⁹ recently published that ACTH has no influence on experimental exophthalmos. These findings are in agreement with his; however, more investigation, which is in process, needs to be done with the purified thyrotropic hormone before concluding that it lacks the exophthalmic factor.

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DISCUSSION

DR. LORAND V. JOHNSON [Cleveland]: I think Dr. Dayton's paper is a distinct contribution, especially his new technique for intercorneal measurements. I do not believe I understood, if he told us, of the basal metabolism rate after the ACTH had been discontinued, or whether that was measured or not.

I would like to ask him whether he thinks that the circumstances leading up to death were thyrotoxic or whether the orbit was in keeping with the thyrotropic type of syndrome.

Studies like this make a very distinct contribution. It follows very closely the findings of Jefferies, who I believe also used DOCA, the preparation following the action of ACTH on the adrenal cortex, and he likewise obtained similar negative results.

DR. JOHN M. McLEAN [New York]: It is interesting to note that a number of observers clinically have attempted to use ACTH, as was apparently done in the clinical case described here, for treatment of progressive postoperative exophthalmos, whereas the essayist, following a clinical case of unsuccessful treatment, has attempted to use it to produce exophthalmos of similar type. As far as I have been able to find out, attempts in either direction to alter the exophthalmic picture have been totally unsuccessful.

Some mention was made of the changes in muscle fibers. This, of course, is what we usually find when muscle is studied, either postmortem or in biopsies, in all these motor sites, although we are inclined to forget that and stress the effect on the extraocular muscles only.

There were some things in the biopsy that interested me very much, particularly the tissue eosinophilia. I would like to ask the essayist about his studies in circulating eosinophilia when the ACTH treatment was used and before it was used. We have seen some effects, not on the exophthalmos but on the by-products of the exophthalmos, in the so-called malignant cases, which are obtainable just as well by the local use of cortisone. That, of course, is simply symptomatic relief with some reduction in the marked chemosis and inflammatory evidence in the eye without any effect on the absolute position of the eye in the skull.

DR. JOHN W. HENDERSON [Rochester, Minnesota]: I agree, as does Dr. McLean, that the use of ACTH in the treatment of malignant exophthalmos has been disappointing. However, we have not seen any case that we thought became worse as the result of the use of ACTH. Much is going to be

gained by studying biopsies from these cases and it certainly is an interesting speculation as to what effect the ACTH might have had on the eosinophilia of the soft tissue in the orbit.

We are not convinced that a true thyrotoxic or thyrotropic type of exophthalmos exists. We are more inclined to regard them all as a degree of the same pathologic process.

DR. GLENN O. DAYTON, JR. (closing): I would like to support what Dr. Henderson said "that we are not convinced that there is a thyrotoxic versus a thyrotropic type of ocular change." However, I think this is commonly taught in quite a number of textbooks and by many clinicians. Clinically and experimentally I agree with him, that exophthalmos, as related to the thyroid, is pituitary in origin. I think that the so-called thyrotoxic pathologic changes in the orbit, which have been reported, have not been substantiated.

As far as the influence of the ACTH on the eosinophilia is concerned, I am afraid that I cannot throw any light on that. I could not explain it in the patient reported.

Regarding Dr. McLean's theory about the myocardium, the muscle findings somewhat resemble what we usually find in the so-called thyrotropic exophthalmos. However, they do differ qualitatively inasmuch as they are more severe. There is actual necrosis of the myocardium and of the extraocular muscles. They also differ quantitatively by the marked eosinophilia. However, in order to show the eosinophilia, we had to use special staining techniques.

The cases that had been previously reported with malignant exophthalmos, in which the patient had died, and there were a few of them, described the extraocular muscles but said nothing about the heart.

Dr. Johnson asked if the pathologic findings in this patient were consistent with the thyrotropic syndrome. No, they were not, because they were more severe. She also had an eosinophilia. If there hadn't been involvement of the extraocular muscles and of most of the skeletal musculature, the pathologic picture in the heart would have been labeled Fiedler's myocarditis.

Dr. Johnson also raised the question as to the basal metabolism rate of the patient after administration of ACTH. It was not done. After thyroidectomy, her basal metabolism rate was plus 15 percent. She had been on some thyroid previous to admission to the hospital.

STUDIES ON THE VISUAL TOXICITY OF METHANOL*

I. THE EFFECT OF METHANOL AND ITS DEGRADATION PRODUCTS ON RETINAL METABOLISM

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(With the technical assistance of Doris Goodman, B.S.)

Cleveland, Ohio

The clinical manifestations of methanol poisoning are adequately described in standard textbooks and the visual symptoms need not be recounted. In regard to incidence, it will suffice to say that six percent of all blindness in a series of World War II veterans was the result of methanol poisoning.¹ The figures for additional fatal cases are not yet available.

The theory of methyl alcohol intoxication, on the other hand, is in a completely unsatisfactory state; and when one looks for the actual toxic agent in methanol poisoning, the toxic mechanism, or the anatomic site, the literature can offer only a series of contradictory statements. Extensive reviews are given by Keeser and Vincke² and by Røe.³

The early idea that methanol toxicity was actually due to impurities in the wood alcohol was soon abandoned,⁴ even before synthetic methanol reached the commercial market and it was found that the symptoms of methanol poisoning were unchanged with it. Nevertheless, a paper naming allyl alcohol as the culprit appeared as late as 1928.⁵

Opposed to this, the theory that methanol itself is the toxic agent has been reiterated in recent years. Mogilnitzkie⁶ claimed that methanol was a specific poison for the autonomic nervous system and Simon⁷ described a specific fractional precipitation of blood proteins by methanol itself as the toxic mechanism.

More numerous have been the advocates

of formaldehyde, a direct methanol oxidation product, as the toxic agent. Among these are Flury and Wirth⁸ who specifically mentioned disturbance of oxidative enzymes as the possible mechanism in visual toxicity, and Keeser and Vincke² who demonstrated the presence of formaldehyde in methanol-liver homogenate.

Contemporaneous with the formaldehyde advocates are those who claim that formic acid formed in the body from methanol is the actual toxic agent and these workers cite the known acidosis of methanol poisoning as proof of their theory.

In 1912, Harnack⁹ claimed toxicity for the formate ion, and more recently Kaplan and Levreault,¹⁰ Røe,³ and Bogen¹¹ have emphasized formic acid and acidosis as the toxic mechanism. Bogen, in addition, discussed the persistence of formic acid in the eye as contrasted to other organs.

The question of the anatomic localization of the ocular damage is also still somewhat unsettled. A number of workers¹²⁻¹⁴ have described damage to the ganglion-cell layer of the retina in humans, but the question of natural autolytic changes has never been satisfactorily answered.

In experimental animals where autolysis has been controlled there are a number of reports of negative retinal findings.¹⁴⁻¹⁷ Røe³ tends to attribute this to a physiologic difference between man and the experimental animals and cites the greater acidosis found by him in man as a parallel and significant species difference. This is by no means established by the work of other investigators.

Finally, the very obvious ophthalmoscopic findings of optic neuritis and later optic atrophy may not be neglected, but whether

* From the Laboratory for Research in Ophthalmology, Western Reserve University. This work was supported by a grant from the Office of Naval Research. A preliminary report on this material was given before the East Central Section of the Association for Research in Ophthalmology, Cincinnati, Ohio, January, 1951.

this involvement is primary or merely secondary to ganglion-cell damage is not clearly established.

In attempting to approach the mechanism of methanol poisoning with a view toward rational therapy, one of the areas of confusion already outlined and amenable to investigation is the nature of the proximal toxic agent. It is this aspect of the problem with which the present paper is concerned.

For purposes of this preliminary study the optic nerve has been temporarily disregarded and the metabolic activity of whole retina, either intact or homogenized, has been the test object. Later, histochemical studies designed to separate the activity of the various layers will only be mentioned in passing.

We believe studies of the whole retina to be justified for preliminary exploration because of the similarity of metabolic activity in all of the central nervous system and the elaborate nature of experiments on separate retinal elements. The effects on selected retinal metabolic activities of methanol, formaldehyde, and formate were measured by standard methods and the results of these experiments are the basis of this report.

METHODS

Single, whole, beef retinas or homogenate equivalent to one retina (for glycolytic experiments one-half retina equivalent) were shaken in a Warburg vessel with air for oxidation experiments and five-percent CO_2 to 95 percent N_2 for anerobic glycolysis experiments. At zero time the appropriate substrate was tipped in from the side arm and oxygen consumption or CO_2 production were measured manometrically.

Substrate concentrations were: acetylcholine, 0.19M, glucose, 0.02M, succinate, 0.02M, hexosediphosphate, 0.004M. Experiments were run for 30 minutes or one hour, depending on rate of reaction. Glucose disappearance was measured by the method of Hoffman;¹⁸ lactic-acid production was measured by the method of Barker and Sum-

merson;¹⁹ triose phosphate was measured by the inorganic phosphate formed (method of Fiske and Subbarow²⁰) by 20 minutes hydrolysis in N/1 potassium hydroxide at room temperature. In the aldolase experiments triose was trapped in a 10-times excess of bisulfate. Acetylcholine was determined by the method of Hestrin.²¹

Inhibitors used were reagent grade methanol, formaldehyde, and formate. Exact formaldehyde determinations were done for free formaldehyde by the method of Tannenbaum and Bricker²² and for total formaldehyde by the dimedon gravimetric method.²³

In this work formate was used instead of formic acid because formate is the natural oxidation product of methanol. The oxidation of a dose of methanol takes place over a period of several days and the body buffers convert the minute amounts of formic acid to formate instantly. Thus at no time is any appreciable quantity of formic acid liberated while a pH compatible with life is maintained.

RESULTS

The activities measured and the concentration of inhibitor to cause 50-percent inhibition of the activity are given in Figures 1 to 4. In Figure 1 is shown the effect of the three inhibitors on oxygen uptake and CO_2 production with no added substrate. It is easily seen that the activity of formaldehyde is 1,000 to 3,000 times that of methanol and 25 to 75 times that of formate.

In Figure 2 where the effect on cholinesterase is pictured, formaldehyde is still the most potent inhibitor but even formaldehyde must be present in 0.06M concentration to cause 50-percent inhibition. No concentrations of methanol or formate which could be readily produced sufficed to inhibit the system significantly. The high resistance of cholinesterase to all three inhibitors makes it an unlikely point of attack in methanol poisoning. In Figure 3, two of the enzyme activities in the glycolytic scheme have been isolated and tested. These are the enzymes

that convert hexose diphosphate to two molecules of phospho-glyceraldehyde. As before, formaldehyde is the most potent inhibitor by over 20 times, but here, too, the formaldehyde dose to give 50-percent inhibition is high.

In Figure 4 formaldehyde effect on a miscellaneous selection of enzyme activities is noted. It should be observed that with glucose as substrate 0.001M formaldehyde inhibits both oxygen uptake and glycolysis by one half. The glycolytic activity has been triply checked by measuring CO_2 production, glucose disappearance, and lactic acid formation and there is agreement between all three determinations.

It should be particularly noted that, in both oxidation and glycolysis with hexose

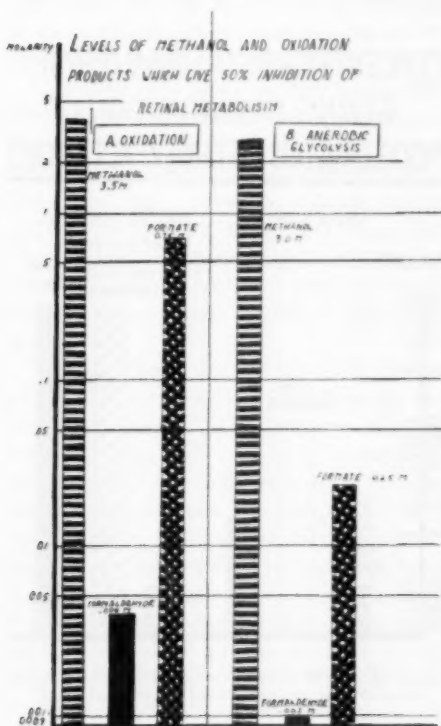


Fig. 1 (Potts and Johnson). The effect of the three inhibitors on oxygen uptake and CO_2 production with no added substrate.

LEVELS OF METHANOL AND OXIDATION PRODUCTS WHICH GIVE 50% INHIBITION OF RETINAL METABOLISM

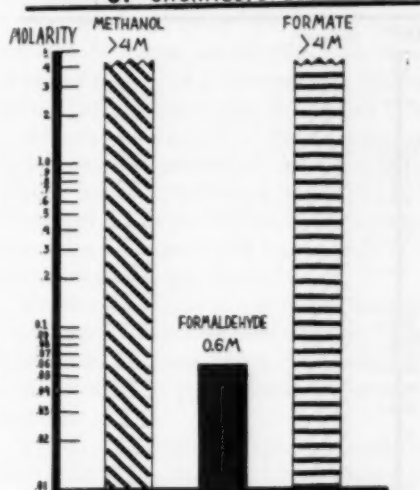


Fig. 2 (Potts and Johnson). The effect on cholinesterase.

diphosphate as substrate, much more formaldehyde is required to inhibit than with glucose; this will be discussed later.

The oxidation of succinate is relatively resistant to inhibition by formaldehyde and, although this is not shown here, it is even more resistant to methanol and formate.

Finally, another isolated glycolytic activity—triosephosphate dehydrogenase—is shown to be inhibited relatively little by formaldehyde.

DISCUSSION

It is ordinarily assumed in the light of recent toxicologic work that the harmful action of a toxic substance is mediated by inhibition of essential enzyme systems in the poisoned tissue.²⁴ Thus, in order to demonstrate the toxic mechanism of a given substance, it must be demonstrated, first, that the substance is capable of inhibiting enzyme systems. Secondly, it must be shown that under actual conditions of poisoning, enzyme

LEVELS OF METHANOL AND OXIDATION PRODUCTS WHICH GIVE 50% INHIBITION OF RETINAL METABOLISM

D. Aldolase (+ triose isomerase)

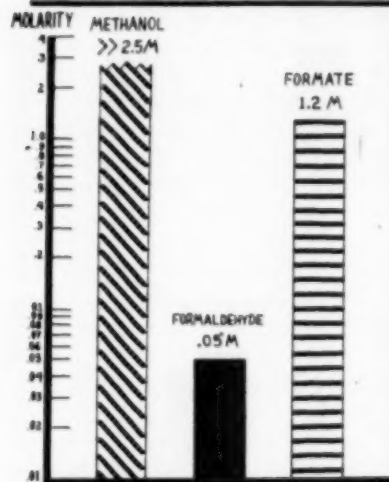


Fig. 3 (Potts and Johnson). Two of the enzyme activities in the glycolytic scheme have been isolated and tested.

inhibitory concentrations are produced in the body.

Finally, it is desirable from the viewpoint of therapy to be able to demonstrate a specific enzyme system or enzyme type which is more susceptible than others to the particular poison in question; for the chemical study of this enzyme type offers hope that a chemical competitor may be designed for the toxin-enzyme reaction; that is, a therapeutic agent.

TABLE 1

THEORETICAL ASPECTS OF METHANOL EYE TOXICITY

Minimum dose of methanol to cause human eye effects	6.0 m. mol./kg.
Dose required for 50% inhibition of retinal glycolysis	
Methanol	3,000.0 m. mol./kg.
Formaldehyde	1.0 m. mol./kg.
Formate	25.0 m. mol./kg.
Dose of acid tolerated by experimental animal in one intravenous infusion ²⁸	26.0 m. mol./kg.

The first and most obvious conclusion from the results presented above is the invariably greater inhibition by formaldehyde of all enzyme systems studied. The decreasing toxicity of formaldehyde > formate > methanol is likewise preserved and the difference in activity between formaldehyde and methanol is for most systems in the order of magnitude of 1,000 times*. This finding is reflected in the systemic toxicities of the substances in question.^{8,25} On this basis one has in formaldehyde a relatively highly toxic substance.

In considering the second criterion, that of adequate toxic concentration, a few approximate calculations will help to clarify the situation. According to Wood and Buller⁴ one to two teaspoonfuls of wood alcohol have caused blindness in authenticated cases.

CONCENTRATIONS OF FORMALDEHYDE GIVING 50% INHIBITION OF MISCELLANEOUS METABOLIC ACTIVITIES

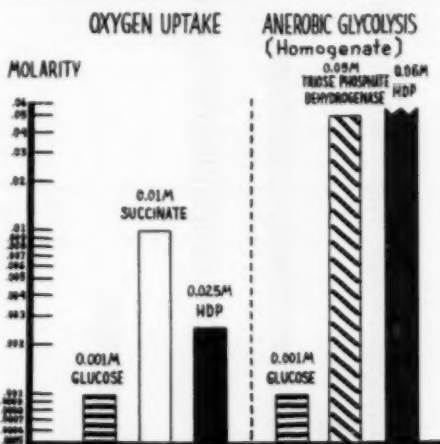


Fig. 4 (Potts and Johnson). Formaldehyde effect on a miscellaneous selection of enzyme activities.

* Since this work was first reported, a paper has been presented confirming the above findings on the metabolism of liver slices. (Watts, D. T.: Federation Proc., 10:343, 1951.

To give ample margin for error, let us call this amount 10 cc. In a 50-kg. patient this, if evenly distributed, would be a final concentration of 5.97 m. mol./kg. Table 1 shows the comparison between this and retinal inhibitory concentrations of the substances studied.

There is no record of any visual effect of acidosis but the systemically tolerated single dose of strong acid is presented for comparison. It is evident that 10 cc. of methanol is far under the inhibitory concentration and even if this were quantitatively converted to formate there would not be enough formate to be inhibitory. If the conversion were instantaneous instead of over a period of days the acid formed would be tolerated easily. Thus, only formaldehyde would be present in inhibitory concentrations and, to give 50-percent inhibition, the conversion of methanol to formaldehyde would have only to be 18-percent efficient.

It is apposite to point out here that the old objection to the formaldehyde theory on the basis of the difficulty of chemically demonstrating formaldehyde in tissue is not a valid one. The very presence of measurable amounts of formate is sufficient proof that formaldehyde is constantly being formed and disappearance is exactly what one would expect of a substance reactive enough to be poisonous.

The third point, that of a specific site of action, also receives some light from the experimental results. It is observed that, in both oxidation and glycolysis, metabolism is more easily inhibited if glucose is the substrate rather than hexose diphosphate. Since, for utilization in either of these two processes, glucose must first be phosphorylated to hexose diphosphate it is logical to assume that this two-step phosphorylation is the most easily inhibited of all the reactions in the metabolic chain. More careful study of these reactions is under way at present.

On the question of anatomic localization of methanol action within the retina, a small amount of preliminary work has been done

using histochemical techniques. So far the formaldehyde inhibition of formazan formation from neotetrazolium²⁷ with a series of substrates has not been found to be confined to a single anatomic layer.

An aside is in order here on the role attributed by recent workers^{2, 28, 29} to formic acid and acidosis in acute methanol intoxication. That acidosis occurs in humans is beyond question. That it is "obviously the condition which is responsible for the death of human beings" (Reference 3, p. 131) is by no means so certain. Not even its strongest advocates have contended that acidosis is responsible for the eye effects.³

Furthermore, Røe in his review contends that experimental animals do not show acidosis to the same degree that humans do, and that death in these animals is not due to acidosis.

Finally, the acidosis which does undoubtedly exist in humans cannot be accounted for on the basis of even complete conversion of a minimum lethal dose of methanol to formic acid over a period of several days. On the basis of blood-formate concentrations only three to 20 percent of the alkali reserve deficit is due to formic acid (Reference 3, p. 111). The explanation given for the acidosis is that the formate-ion inhibits "oxidase."

We have shown that formaldehyde is a much more potent inhibitor of oxidation in retina than is formate, but it is even a more potent inhibitor of glycolysis. Thus, the inhibitory phenomenon which is considered to be the cause of the acidosis by its proponents is not demonstrable *in vitro*. The acidosis itself may only be used to account for death in man but not for death in experimental animals or eye effects in either—an extremely unlikely situation.

SUMMARY

1. The inhibitory effect of methanol, formaldehyde, and formate has been measured on a number of the enzymic reactions of surviving beef retina.

2. In all cases so far investigated formal-

dehyde is the most potent inhibitor of the three substances tested—by at least an order of magnitude over formate and by two to three orders of magnitude over methanol.

3. The enzymic process most sensitive to formaldehyde inhibition is glycolysis. Under our conditions 0.001M formaldehyde gave 50-percent inhibition of retinal glycolysis.

4. Preliminary studies indicate that the site of inhibition of glycolysis lies in one or both of the phosphorylation steps.

5. Early results with tetrazolium salts show no anatomic localization of formaldehyde inhibition.

6. By approximate calculation from the inhibitory concentrations of the three sub-

stances tested and from the minimum dose of methanol known to cause eye effects, only formaldehyde is likely to be present in inhibitory concentrations after such a dose.

7. The postulates of formate activity on tissue "oxidase" of previous workers are not substantiated by the present work, and the role of acidosis is a highly questionable one.

8. From the material presented above, we believe that the proximal toxic agent in methanol poisoning is formaldehyde.

University Hospital (6).

The discussion of this paper will be found on page 123.

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STUDIES ON THE VISUAL TOXICITY OF METHANOL*

II. THE EFFECT OF PARENTERALLY ADMINISTERED SUBSTANCES ON THE SYSTEMIC TOXICITY OF METHYL ALCOHOL

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This study is a portion of a lengthier investigation of various substances and factors which may possibly influence the course of methanol poisoning in the whole animal. It approaches from another direction the problems posed in paper I of this series.¹

The use of the whole animal rather than the eye, or portions thereof, is one approach to the problem of the proximal toxic agent in methanol poisoning; for either an increase or a decrease in toxicity caused by a specific substance throws added light on the toxic mechanism. This approach presents the added feature that, in its course, a therapeutic agent may be found more readily.

The study is based on the assumption that at least some of the systemic and eye effects are the same. The mechanisms of systemic and ocular toxicity of methanol are equally unknown, and systemic effects

can be investigated much more readily in experimental animals.

This report is concerned specifically with the influence of tetraethyl thiuramdisulfide (antabuse), glycine, cysteine, cortisone acetate, and ethyl alcohol on the course of methanol poisoning in the mouse.

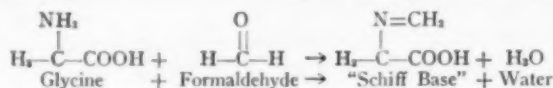
Antabuse was studied in an endeavor to clarify the mechanism of methanol toxicity from a new direction. Methanol in the body is oxidized to formaldehyde, then to formic acid, and then—but very slowly—to carbon dioxide and water.^{2,3} Ethyl alcohol likewise is oxidized first to acetaldehyde, then acetic acid, and finally to carbon dioxide and water.^{4,5} In contrast to the behavior with methanol, this last reaction occurs rapidly.

It has been shown by the original investigators⁶ that antabuse inhibits the activity of aldehyde oxidase which is necessary to convert acetaldehyde to acetic acid, and that the piling up of the aldehyde causes the increase in toxic symptoms. Since the aldehyde oxidases for both acetaldehyde and formaldehyde are believed to be the same,⁷ antabuse might be expected to inhibit formaldehyde

* From the Eye Service, Department of Surgery, University Hospitals, and the Laboratory for Research in Ophthalmology, Western Reserve University. This work was aided by a grant from the Office of Naval Research. A preliminary report on this material was given before the East Central Section of the Association for Research in Ophthalmology, Cincinnati, Ohio, January, 1951.

oxidase and cause a piling up of formaldehyde, resulting in an increase in the toxicity of methanol.

Our investigation of amino acids for possible antagonistic action against methanol is based on the hypothesis that Sørensen's formal titration works in the animal as well as in the test tube. The generally published formulation for the amino acid-formaldehyde reaction is as follows:



However, neither the formulation nor the stability of the Schiff's base are firmly established.

Ratner and Clarke⁸ demonstrated that cysteine combined with formaldehyde to form a stable, cyclic compound, thiazolidine-4-carboxylic acid. Cysteine therefore looked promising for trial as an antidote to methanol poisoning because of its formation in vitro of such a stable compound with formaldehyde.

Cortisone acetate has proven effective against a number of toxic substances; consequently its possible effects against methanol were tested in a small series of animals.

In their clinical application, the ethyl-alcohol studies are most important. In a paper in 1943,⁹ and in his 1946 *Acta Medica Scandinavica* monograph on methanol poisoning,¹⁰ the Norwegian ophthalmologist, Røe, urged the use of ethyl alcohol in the therapy of methanol poisoning. Røe emphasizes the following statements:

"One can hardly doubt that the consumption of ethyl alcohol just before or during methanol poisoning is the chief cause of the great tolerance shown by some individuals. . . .

"The fact that even severe symptoms quickly vanish after the consumption of ethyl alcohol late in the course of the poisoning (see case nr. 17) shows that ethyl alcohol not only arrests the further increase of acidosis, but also reduces it."

Røe defines as the latent period, "the interval between the onset of poisoning and the appearance of clinical manifestations."

He also claims that ethyl alcohol affects the latent period favorably, saying, "Prolongation of the latent period beyond 24 hours is always due to the consumption of ethyl alcohol."

Røe's conclusions were based entirely on clinical impressions of cases singled out from his larger series, with no adequate controls. However, the results of Zatman,¹¹ demonstrating in vitro inhibition of methanol

oxidation by ethyl alcohol, lend plausibility to the theory. Because of Røe's publications, ethyl alcohol has since been administered therapeutically in methanol poisoning of United States Navy personnel.¹²

Although ethyl alcohol has been found to have a synergistic action with methanol on the isolated enzyme system of xanthine oxidase¹³ and on the behavior of rats in a maze,¹⁴ to our knowledge, no previous controlled studies have been made with acute toxicities.

MATERIALS

Mice. Young adult, presumably male, Swiss albino mice from the Albino Farms were used. They were fed a diet of "Fris-kies."^{*}

Methanol. Absolute methanol (Merck reagent) was diluted with two volumes of distilled water, and the resultant solution was used for injection.

Formaldehyde. Thirty-seven percent (by weight) formaldehyde (Merck) was used. Standardization by the method of Tannenbaum and Bricker¹⁵ showed two thirds of this to be "free." One hundred percent of the material was available for precipitation by dimedon in the usual gravimetric determination.¹⁶ Solutions for single injections producing the approximate L.D.₅₀ were made to contain 3.17 mg. "free" formalde-

* Dog biscuits made by Albers Milling Company.

hyde/cc. Somewhat stronger solutions were prepared for higher dosages.

Antabuse. This was administered in four-percent solution containing one-percent gelatin (U.S.P.).

Glycine. A five-percent aqueous solution was used.

Cysteine. The free base was obtained from Nutritional Biochemicals Corporation and made into a 1.8-percent aqueous solution. Because of the instability of cysteine in water,¹⁷ fresh solutions were made immediately prior to each injection.

Thiazolidine-4-carboxylic acid was prepared by Dr. John W. Patterson by the method of Schubert.¹⁸ An aqueous solution containing 20 mg./cc. was used for injections.

Cortisone acetate. The Merck suspension was diluted with a one-percent by weight aqueous gelatin solution to make solutions containing 0.4 mg. and 0.6 mg. cortisone/cc.

Ethyl alcohol. Ninety-five-percent ethyl alcohol was diluted to make aqueous solutions of the following concentrations:

a. Twenty percent by weight for experiments using 2 gm./kg. mouse.

b. Four percent by weight for experiments using 0.674 gm./kg. for the first injection and 0.404 gm./kg. for subsequent ones.

c. Two percent by weight for experiments using 0.17 gm./kg.

In general, the strength of the various solutions was selected with the object that the volumes injected be sufficiently large for accuracy of measurement and sufficiently small that the total intraperitoneal injections at one time would not harm the mice. The pH of all solutions was between 7.4 and 6.2, except for thiazolidine-4-carboxylic acid which was approximately 4.5.

METHODS

All substances were administered by intraperitoneal injections. Methanol and formaldehyde were given in a single dose so

that the experiments would deal with acute toxicities. The modifying substances were given at time intervals varying to permit maintenance of their body levels for the first two days following introduction of the toxic agent.

Mice were weighed prior to their initial injections, marked if necessary, and individual inoculations calculated on the basis of individual weights.

When methanol or formaldehyde was used in amounts in the region of the L.D.₅₀, controls of these toxic substances were run with every experiment. In a few instances when amounts of methanol less than the minimum lethal dose were used, and in one other case (Experiment 14) the controls were not run simultaneously.

The dosages of the modifying substances studied were sublethal and, in most cases, subtoxic, with a few exceptions noted in the individual sections.

RESULTS*

I. METHANOL

Albino mice were given single intraperitoneal injections of methanol. Figure 1 shows the typical, sigmoid toxicity curve obtained from our results. Each dot represents the results obtained from the use of from five to 10 mice. The number of mice for each dot averaged nine.

All mice receiving 4.0 gm./kg. survived; they showed slight ataxia for less than an hour following injection, but none exhibited narcosis. At 5.5 gm./kg. the mice displayed ataxia with, or without, light narcosis.

Criteria of light narcosis are the following signs described by Munch and Schwartz:¹⁹ stupor and immobility except in response to pain. Also by the definition of the same authors, deep narcosis produces the clinical picture of comatose animals with

* The data are presented in graphic form. Protocols of any experiments reported in this paper may be obtained on application to the authors.

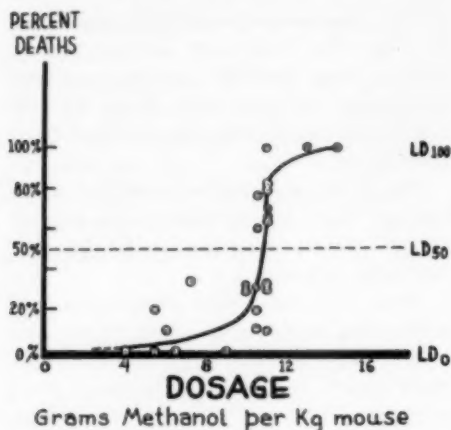


Fig. 1 (Gilger, Potts, and Johnson). Acute toxicity from methanol in white mice.

absent pain and corneal reflexes and with occasional involuntary reflex motions in some animals.

By 7.3 gm./kg. some mice were in deep narcosis following injection; the rest were in light narcosis. From a level of 10.0 gm./kg., or higher, the mice usually enter into deep narcosis within a few minutes following injection. A portion died without recovering from deep narcosis; others recovered, but ultimately died; the rest survived.

Fatal terminations following recovery from deep narcosis usually occurred within 24 hours after injection. As a rule, survivors became normal and active by the end of 48 hours. The return of the fur to its usual sleek appearance was the last step in rehabilitation.

From a level of 10.0 gm./kg. and higher, the interval between introduction of methanol and occurrence of death was roughly inversely proportional to the amount of methanol. Four out of 203 mice receiving 11.0 gm. methanol/kg., or less, died within 30 minutes after injection. They were excluded since death was explicable on the basis of injection trauma (for example, ruptured spleen). No deaths which we considered at-

tributable to methanol occurred later than four days following injection.

II. FORMALDEHYDE

Figure 2 portrays formaldehyde toxicity. Each dot represents the results obtained from the use of from four to 10 mice. The number of mice for each dot averaged eight. The approximate L.D.₅₀ was 0.07 gm. formaldehyde/kg. mouse.

The clinical course varied considerably from that following methanol. With higher amounts of formaldehyde (0.10 gm./kg. or more), immediate toxic signs of tonic convulsions, opisthotonus, and death in respiratory failure occurred, the time interval between injection and death being roughly inversely proportional to the dosage.

At levels causing an approximate 50-percent mortality, the mice usually were apparently normal the first 24 hours, becoming progressively more ill during the next few days, and then either recuperating or dying.

Deaths referable to formaldehyde occurred up to the seventh day following injection. It should be noted that, despite the known high reactivity of formaldehyde, there was no sign of local activity on the peritoneum when autopsies were performed.

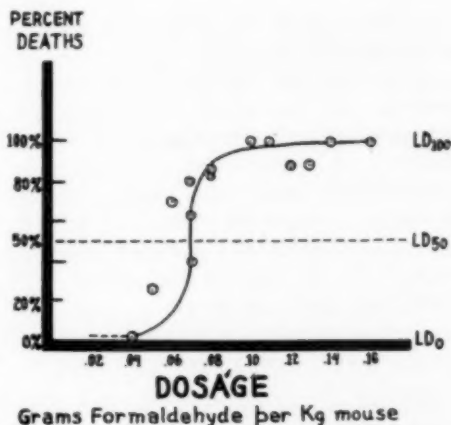


Fig. 2 (Gilger, Potts, and Johnson). Acute toxicity from formaldehyde in white mice.

III. ANTABUSE

Our results with antabuse are shown in Figure 3. Each square represents the results obtained from the injection of both methanol and antabuse in groups of from three to eight animals. The average number of mice per square was six. The amounts of antabuse given were below the minimum lethal dose for white mice.

Hanzlik and Irvine²⁰ found the lethal dose of antabuse in dogs and rabbits to be 3.0 gm./kg. Hald, Jacobsen, and Larsen²¹ gave rats 0.025 gm./kg. intraperitoneally every day for several months with no deaths and found mice showed no symptoms after a single dose of 0.6 gm./kg. intraperitoneally. (They report no single injections of higher amounts.)

The sublethal amounts of antabuse which we used exerted a potentiating action on methanol, causing the L.D.₅₀ to occur at approximately half the dosage giving a 50-percent mortality with methanol alone. This was 5.5 gm. vs. 10.5 gm.

IV. AMINO ACIDS

A. Glycine. Glycine, 1.25 gm./kg., was administered every day for three days. This

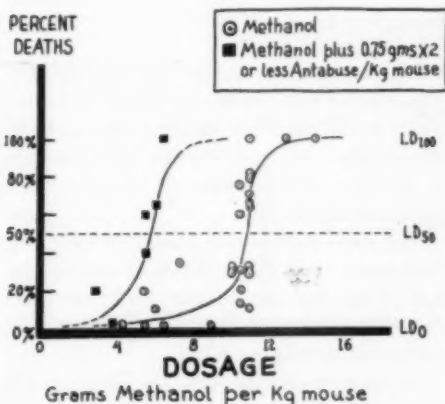


Fig. 3 (Gilger, Potts, and Johnson). Effect of antabuse on acute toxicity from methanol in white mice.

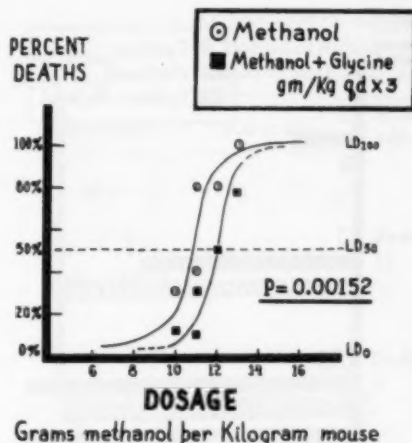


Fig. 4 (Gilger, Potts, and Johnson). Effect of glycine on acute toxicity from methanol in white mice.

amount of glycine alone caused neither deaths nor toxic symptoms in our mice.

Sullivan, Hess, and Sebrell²² found a diet containing 10-percent glycine was compatible with life for at least 15 days in the white rat. Jovanovic²³ found that 12.5 gm. glycine/kg. white mouse produced death within 24 hours.

In our experiments, the first injection of glycine was given just prior to the methanol injection. Figure 4 shows that glycine had a slight but mathematically significant* action against methanol. For better graphic representation, only results from the methanol controls run simultaneously with the glycine have been charted. The probability given in the figure is derived from the charted data.

When these glycine results are compared with the total methanol results of this study in the dosage range including 10.0 to 13.0 gm./kg., the probability that the antidotal action of glycine is due to chance is 0.00104.

Each square in Figure 4 represents the results obtained from the injection of both

* Statistical significance has been determined in this study by the method of exact probabilities.

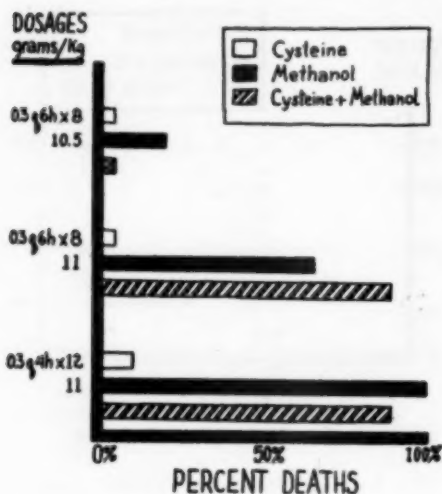


Fig. 5 (Gilger, Potts, and Johnson). Effect of cysteine on acute toxicity from methanol in white mice.

glycine and methanol in groups of from nine to 10 mice. The protective action of glycine amounts to approximately a gram of methanol per kilogram mouse.

A preliminary experiment indicated that glycine may possibly have a similar marginal protection against formaldehyde.

B. Cysteine. Figure 5 shows the results when varying amounts of cysteine were used with methanol. The highest dosage of cysteine, 0.3 gm./kg. (every four hours, 12 times), resulted in a 10 percent mortality. The other doses were sublethal. Each diagonally striped line represents the results obtained from the injection of both methanol and cysteine in from eight to 10 mice. Essentially no effect was exerted by cysteine on methanol toxicity.

Cysteine was therefore tried in conjunction with formaldehyde. Formaldehyde at a level causing an approximate 50 percent mortality was injected intraperitoneally within 15 minutes following 0.30 gm. cysteine/kg. mouse. This resulted in a rapid and dramatic death of 100 percent of the mice within two hours.

Clinical signs appeared approximately 10 minutes following the formaldehyde. They were those of hyperexcitability with mice running and jumping madly around the cage, tonic convulsions, terminal hyperextension of the extremities, and frothing at the mouth.

Out of the 10 animals, the five dying after 30 minutes showed oral and/or nasal hemorrhage, starting with slight staining and ending with massive hemorrhage in the last three mice to die.

Gross autopsies performed by Dr. D. Chickering showed no immediate cause of death except in the case of the last mouse to die, where exsanguination was the immediate, or contributing, cause of death.

Pure thiazolidine-4-carboxylic acid was injected intraperitoneally, 0.33 gm./kg., into two mice. Both died within 20 minutes, following clinical signs identical with those exhibited by mice receiving formaldehyde and cysteine separately.

V. CORTISONE ACETATE

From a total dose of 24 or 50 mg. cortisone/kg. mouse, given in divided doses over three days, there was no effect on the mortality caused by 11.0 gm. methanol/kg. mouse.

VI. ETHYL ALCOHOL

Figure 6 shows that in our experiments ethyl alcohol significantly increased the toxicity of methanol. Each square represents the results obtained from the use of from five to 10 mice. The number of mice for each square averaged eight.

The ethyl alcohol was administered every four hours until either the death of the animal or the end of 48 hours, with the first dose given a few minutes prior to the single methanol injection.

In the experiments shown in Figure 6, 2.0 gm. ethyl alcohol/kg. mouse were injected. The mice on this amount became ataxic but did not show narcosis.

Ethyl alcohol changed the L.D.₅₀ of meth-

anol from 10.5 to 5.5 gm. When a lower level of methanol, namely 6.0 gm./kg., was injected (LD_{10} on the control curve), ethyl alcohol gave an average 80 percent mortality, which change is statistically significant. The same dosage of ethyl alcohol likewise increased the mortality resulting from formaldehyde from 40 to 100 percent.

The experimental data for the effect of ethyl alcohol on formaldehyde poisoning is presented in Table 1.

Using the same interval and duration of injections, we administered an initial dose of 0.674 gm. ethyl alcohol/kg. and succeeding doses of 0.404 gm./kg. This level of ethyl alcohol given alone produced no toxic signs.

The control group given 11 gm. methanol had a 40 percent mortality. The group given the same amount of methanol plus ethyl alcohol had a 100 percent mortality. Thus, this level of ethyl alcohol also caused a significant increase in the number of deaths from methanol.

A dosage of 0.17 gm. ethyl alcohol/kg. was given, every four hours, 12 times, to mice also given 10.5 gm. methanol. This amount of ethyl alcohol increased the deaths from

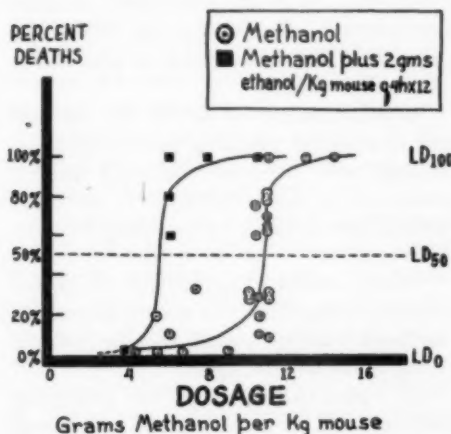


Fig. 6 (Gilger, Potts, and Johnson). Effect of ethyl alcohol on acute toxicity from methanol in white mice.

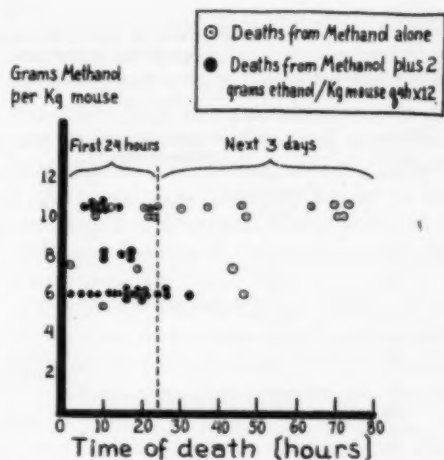


Fig. 7 (Gilger, Potts, and Johnson). Effect of ethyl alcohol on time of death from single methanol injections in white mice.

the methanol by almost 40 percent. The increased toxicity using 0.17 gm. had an exact probability of chance occurrence of two parts in 100. The experimental data for the last two levels of ethyl alcohol are presented in Table 1.

In our experiments the only measurable time element was the time at which deaths occurred. This is shown in Figure 7. Each dot represents one dead mouse. There are fewer dots in the lower part because very few animals died from those amounts of methanol.

The schedule of injections every four hours permitted frequent enough observation for sufficient accuracy of the times of death. The methanol-plus-ethyl-alcohol mice were almost all dead before the first control methanol mouse died.

The chart is divided for statistical purposes into the first day and the next three days. The predominance of the ethyl-alcohol mice in the first day can be readily seen. This finding that ethyl alcohol hastened the time of death from methanol in mice is statistically significant.

TABLE 1
THE EFFECT OF ETHYL ALCOHOL ON THE ACUTE TOXICITIES OF
METHANOL AND FORMALDEHYDE IN WHITE MICE

Experiment Number	Dosage			Results			
	(Grams per kilogram given intraperitoneally)			Number of Mice			
	Formaldehyde	Methanol	Ethanol*	Living	Dead	Total Used	Percentage Deaths
41	—	—	2.0	10	0	10	0%
35	0.07	—	—	6	4	10	40%
35	0.07	—	2.0	0	10	10	100%
41	—	—	0.67×1 0.40×11	10	0	10	0%
36	—	11.0	—	6	4	10	40%
36	—	11.0	0.67×1 0.40×11	0	9	9	100%
17	—	10.5	—	8	1	9	11%
17	—	10.5	0.17	5	5	10	50%
14	—	10.5	0.17	1	4	5	80%

* Dosage given in each injection. The first injection of ethyl alcohol was made just prior to the single methanol or formaldehyde injection. Ethyl alcohol was given every four hours thereafter for a total of 12 times unless the mouse died before completion of the course of injections.

DISCUSSION

The L.D.₅₀ for single, intraperitoneal injections of methanol in white mice was found to be 10.5 to 11.0 gm./kg. Acute toxicity figures for methanol in mice were not found in the available literature.

Alder, Buschke, and Gordonoff²⁴ in a small series of white rats found 75 percent mortality from 8.4 gm. methanol/kg. per os. Munch and Schwartz¹⁹ culled many figures for various species from the literature. Our findings for the L.D.₅₀ in the white mouse are in line with those for other species.

The approximate L.D.₅₀ for single, intraperitoneal injections of formaldehyde in white mice was found to be 0.07 gm./kg. Here, too, there were no available toxicity figures for white mice in the literature. Sollmann and Hanzlik²⁵ report the minimum lethal dose in the rabbit to be 0.09 gm./kg., intravenously, and in the dog to be 0.07 gm./kg., intravenously. Our finding is consistent with this.

In equimolar amounts formaldehyde was 145 times as lethal as methanol.

Antabuse was found to increase the toxicity of methanol. While our experiments were in progress, Way and Hausman²⁶ reported that antabuse administered for three days prior to methanol decreased its oral L.D.₅₀ in rats and rabbits.

In the introductory section we outlined our reasons for assuming that antabuse, in analogy with its action on ethyl alcohol, blocks the biologic oxidation of methanol beyond formaldehyde by inhibiting the aldehyde oxidase.

This assumption, together with the experimental finding that antabuse potentiated methanol toxicity, makes formate unlikely as the proximal toxic agent.

Of the two possibilities remaining, methanol and formaldehyde, the latter seems the more likely one in view of evidence presented in the preceding paper of this series.¹

The slight protective action of glycine

against methanol poisoning is insufficient to advocate clinical use of glycine; but the finding that the protective action is of a mathematically significant degree leads us to believe that further work with competitive compounds is indicated, and also lends additional support to the formaldehyde hypothesis.

Cysteine produced no effect on methanol poisoning and markedly potentiated the toxicity of formaldehyde.

Thiazolidine-4-carboxylic acid, which is produced by the *in vitro* reaction of cysteine with formaldehyde, caused the same toxic signs and lethal effects as separate injections of cysteine and formaldehyde in the mice. Thiazolidine-4-carboxylic acid is apparently, in itself or in its oxidation products, a highly toxic substance.

That cysteine did not significantly increase the toxicity of methanol may possibly be due to differences in the times and amounts of formaldehyde distributed intra- and extracellularly following intraperitoneal injections of methanol and formaldehyde.

The effect of three different dosage levels of ethyl alcohol on methanol poisoning was tested in mice because ethyl alcohol has been advocated and used clinically as an antidote for methanol poisoning. The highest level, 2.0 gm. ethyl alcohol/kg., significantly increased the mortality resulting from methanol and formaldehyde. It also significantly shortened the time between injection of and death from methanol. This was our only measurable time element.

In contrast to our findings is Røe's statement¹⁰ that ethyl alcohol increased the latent period of methanol poisoning, the latent period being the only time element with which he makes an association with ethyl alcohol. This highest ethyl alcohol dosage translated to humans is roughly equivalent to 350 cc. of 100-proof whiskey—a large dose but not above chronic alcoholics' claims.²⁷ It is higher than the several amounts of ethyl alcohol given therapeutically.

Røe¹⁰ advocated an initial dose of 0.674 gm. ethyl alcohol/kg. and succeeding doses equivalent to 0.404 gm./kg. every four hours thereafter until the patient's recovery or demise. Our second dosage level was therefore this amount, ending, however, at 48 hours to maintain conditions similar to the rest of our experiments. It also produced a significant increase in the number of deaths from methanol.

The Navy¹² followed Røe's advice to give ethyl alcohol, but administered less than half the dose that Røe advocated, giving an ounce of whiskey every four hours for a "day or two."

On the assumption that the whiskey was National Formulary,²⁸ and the men weighed 70 kg., this dosage is equivalent to 0.17 gm. ethyl alcohol/kg. mouse every four hours for two days. The increase in methanol deaths in our experiments from this lowest dosage of ethyl alcohol was only probably significant.

Although experiments with lower animals cannot be assumed to have complete application to human beings, our findings that ethyl alcohol increases the toxicity of methanol in white mice, together with the lack of any controlled clinical evidence to the contrary in humans, makes it seem reasonable to urge that the use of whiskey in patients with methanol poisoning be discontinued until more definite evidence is available.

SUMMARY

1. The acute toxicity of methanol and formaldehyde for white mice has been determined. The L.D.₅₀ for single intraperitoneal injections of methanol was between 10.5 and 11.0 gm./kg. The L.D.₅₀ for single intraperitoneal injections of formaldehyde was around 0.07 gm./kg.

2. Antabuse increased the toxicity of methanol by approximately two times.

3. Glycine protected against methanol poisoning, significantly but slightly. Cysteine did not counteract methanol poisoning. In addition, it apparently formed a highly toxic

compound with formaldehyde.

4. Under our experimental conditions, cortisone had no effect on methanol poisoning.

5. Ethyl alcohol significantly increased the toxicity of methanol and formaldehyde and significantly lessened the time of death following methanol poisoning. Under our experimental conditions and with white mice, ethyl alcohol, a substance which has been

recommended and used as an antidote for methanol poisoning, is definitely harmful from the point of view of life itself. For this reason, use of ethyl alcohol in the therapy of human methanol poisoning should be discontinued pending further investigation.

University Hospital (6).

We wish to thank Miss Mildred Orchen for technical assistance, and Ayerst McKenna and Harrison Ltd. for our supply of antabuse.

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DISCUSSION

DR. VIRGIL C. CASTEN [Boston]: Far be it from me to give you any chemistry of this serious situation but I have seen probably about 40 cases of methanol poisoning, most of them too late to be helped by medical aid, that is, almost blind, with primary optic atrophy and large central scotomas. But I did happen to observe the care of six or eight men brought in in coma, having taken a considerable, unknown quantity, of wood alcohol or methanol. These patients were treated as a patient in diabetic coma. Now, diabetic coma is a condition of insufficient insulin and giving large doses of insulin usually relieves the coma. That is not the situation, however, in methanol poisoning. It was our contention, however, that it was one of acidosis and we treated it by correcting the acidosis.

These patients were given large doses of sodium *r*-lactate (one-sixth molar solution) intravenously in isotonic solution of three chlorides. They were given considerable amounts of sodium bicarbonate (about four gm. every 15 minutes per four doses) in the stomach by gavage if necessary and put into oxygen tents. In 24 hours they were all conscious. They all had papilledema, and edema of the surrounding retina like a neuroretinitis.

Their eyes were kept bandaged to keep the light out—purely empirically. I am not sure that is necessary or even desirable, but it was done. These 26 patients all regained their vision and, within a week, not one of the group had less than 20/40 vision and they all got back to 20/30 or even 20/20, with one exception.

This work was reported by Dr. E. H. Berger, of Portland, Oregon, Dr. William Chew of Berkeley, California, and Dr. M. Capron of Battle Creek, Michigan, from a medical point of view (*J.A.M.A.* 1946, p. 61).

They took the CO_2 combining power every two hours, I think, roughly, the first little while. The test takes about half an hour to run so you can't do it too often. You have to be very careful that you do not give too much alkali and throw them over on the other side. That was their problem; they did not know how much alkali or how much sodium bicarbonate to give intravenously, because they were afraid of producing the opposite effect, and that is why they were taking CO_2 combining powers as often as possible.

I think the essayists are to be congratulated on their work in trying to pinpoint the toxic metabolite that affects the optic system; to pinpoint the

exact point, whether it is the optic nerve, center, or the ganglion-cell layer.

I cannot add anything about the chemistry but if anyone of you get one of these patients in the acute state, in coma, if you will get the help of one used to treating diabetic coma and start on that basis, I think you will go a long way toward saving his life and eyesight.

Treatment: First, draw blood for the plasma carbon-dioxide combining power. This may be down to 10 volumes percent.

Second, administer alkali immediately: (a) Give four 40-cc. ampules of sodium *r*-lactate molar solution in one liter of isotonic solution of three chlorides and give intravenously; (b) give four gm. of sodium bicarbonate by mouth every 15 minutes for four doses. After giving the alkali, check the blood-plasma bicarbonate. Then repeat the alkali. Perhaps, this will be necessary three or four times to change the carbon-dioxide combining power from 10 to 20 volumes percent to 40 to 50 volumes percent. At this point it can be checked twice daily until recovery.

DR. P. J. LEINFELDER [Iowa City]: Methyl-alcohol poisoning brings up a number of problems that will require further research to explain. One is the variations in individual response, since in some instances very small quantities of methanol will cause severe intoxication and death, while in other instances the ingestion of large quantities seems to be relatively harmless.

The second point is an explanation of the pathologic changes; and almost interrelated is the third point, mode of action of the poison.

The ocular events that follow the ingestion of methanol indicate a selective injury to the nerve cell, in this instance the ganglion cell, which can be affected either partially so that there is an impairment in its function over a period of time; or completely in which function is completely and permanently destroyed because of death of the cell.

Impairment of function comes on relatively late after ingestion, within several hours, or quite suddenly. This is in accord with what is known of the action of various inhibitors on the activity of the nerve cell, for in some instances the ganglion cell can be affected so that there is complete and irrevocable loss of vision, while in other instances it may be transient and partial.

This is well illustrated by the common occur-

rence in retrobulbar neuritis in which, for considerable periods of time, there may be complete cessation of activity of the ganglion cell and its neuron but, after a period of time, recovery occurs with return to normal vision.

Histologically, this is identified with the changes that occur in retrograde degeneration of the ganglion cell. Sometimes there is complete dissolution of the ganglion cell but sometimes only the reaction to injury occurs and then a restitution of its normal appearance, even though function may not return (in severance of the axon).

The argument presented by the essayists is, I think, excellent. I am particularly happy to see that the essayists are not satisfied with the overworked word "toxin." They wish to explain, as should always be explained, what physiologic changes occur to produce the pathologic changes after exposure to various substances.

More important than the demonstration of the possible role of formaldehyde is the great step that the authors are making in attempting to point out that there is some specific effect on the enzyme systems of the cell that will result in impairment of function and possibly in death.

I have appreciated the paper very much. I believe none of us are in a good position to explain or to criticize any of their work because we have not read the paper. However, I wonder whether there isn't a little reaching when you make the calculations on the basis of the minimum dose of methanol; and I also wonder whether there is not a little difficulty when you attempt to interpret the effects of two toxic agents on a mouse, the two toxic agents being ethyl alcohol and methanol or antabuse and methanol.

I thank you, I appreciated the paper, I am very happy at the steps you have taken to improve the scientific approach to this problem.

DR. JONAS S. FRIEDENWALD [Baltimore]: I want to add only a very few words to this discussion. In the first place, I think these two papers are a perfectly beautifully organized study and it has been a thrilling experience to listen to this very systematic and illuminating study.

The raising of this subject takes me back to the days of my youth because the very first study that I ever made in medical research was when I was a medical student, and a fellow student and I attempted to find out something about the mechanism of wood-alcohol poisoning.

We were at that time under the erroneous notion that perhaps formic acid or formate might be the toxic agent and we set out to test that on experimental animals. What we found was absolutely zero; that is to say, we poisoned all manner of laboratory animals that we could get our hands on with methanol. In no case were we able to demonstrate any injury to the visual apparatus. There was no optic atrophy; there were no changes in the retina; the previously described changes in the Nissl bodies which Birch-Hirschfeld had published

20 years before that (50 years ago now), we were unable to confirm.

What impressed us at the time, and what I think is still an important consideration, is that there are enormous species differences in the toxicity of this compound. We did not try cattle so I cannot say whether retinal changes could be produced with methanol in cattle, but we were unable to produce any retinal changes in dogs, cats, rabbits, guinea pigs, mice, rats, and chickens. I think that was the limit of our zoölogy.

At any rate, I think it would be extremely interesting if studies of the type that Dr. Potts has been making could be done on human retina, which is, after all, occasionally available in biopsy, and particularly as to whether there is any difference between Negroes and Caucasians in this matter, because there certainly is a very large difference in the tolerance of Negroes and whites for methyl alcohol. Methyl alcohol, at least in Baltimore, is very widely consumed by the Negro population and yet the incidence of methyl-alcohol toxic symptoms in the Negroes is extremely low. In fact, I have only seen, myself, one case of methanol optic atrophy in the Negro.

DR. DAVID G. COGAN [Boston]: Dr. Grant is not here but I would like to represent him, however poorly, because I believe he views these things a little differently. He produced optic atrophy in the rabbit with methanol. I think he probably used a large amount and maybe that is the difference between his and Dr. Friedenwald's observations, but he did produce optic atrophy which was quite evident in the absence of pupillary reaction and also the optic atrophy of the nerves subsequently. He was interested in determining whether or not formaldehyde might be the mechanism of action.

He then attempted to produce blindness by injecting formaldehyde with doses far in excess of that which could occur from the transmutation of the methanol that had been given, and found that it did not produce blindness. I believe I am quoting him correctly in saying that he concludes that, in the living rabbit at least, formaldehyde was not responsible for the blindness of methanol poisoning.*

MR. GORDON L. WALLS [Berkeley, California]: Apropos of Dr. Leinfelder's and Dr. Friedenwald's remarks concerning the variability of response, the second essayist seemed to be saying that a little increase in dose produced a marked increase in effect on the individual mouse, but the curves that she showed seemed clearly to be probability integrals, implying that, in the mouse, there is "normal" individual variation in sensitivity to methanol. It looks, then, as though it should not

*In subsequent discussion with Dr. Grant I learned that blindness from methanol had occurred in one rabbit only and that it was his opinion that methanol toxicity could be attributed to formaldehyde formation. (D.G.C.)

be hard to breed pure strains of mice with either a high and standardized or low and standardized sensitivity, if this should seem desirable in the continuation of this program.

Another point, methyl salicylate in carload lots is consumed in this country annually in the form of athletic rubs and linaments for the relief of pain. When absorbed through the skin, methyl salicylate is hydrolyzed into salicylic acid and methanol. I should like to ask the essayists if they suspect that the amount of formaldehyde thereupon formed is possibly harmful.

DR. WALTER H. FINK [Minneapolis]: Some years ago I performed a series of experiments on animals of various types, including the monkey. In addition, I was fortunate enough to obtain the eyes of two humans at the time of death. According to the literature, most of the specimens obtained in the past have been from cadavers that have been dead for some hours and possibly post-mortem change has taken place.

The reason I was interested in the subject was because of the controversy as to whether the optic nerve or the retina is primarily affected. In my experiments, I used formic acid, in addition to other drugs, and I found changes comparable to methyl alcohol in the monkey, the dog, and the rabbit and I concluded that formic acid was a toxic factor.

The human specimens were examined microscopically by Dr. Leinfelder and showed edema of the optic nerve and also changes in the retina, indicating a simultaneous process.

I wonder whether we can compare animal experimentation in a subject of this type to the human. Individual susceptibility is a marked factor in the human. Some people can take this without any ill effects; others, with a small dose, are seriously affected and permanently lose vision; in others it must have a cumulative effect.

I feel we have much to do before we have answered the question. I, personally, as a result of these studies, feel that the poison has a special affinity to highly differentiated tissue, and that the retina and the optic nerve can be simultaneously affected.

DR. ALBERT M. POTTS (closing): I would like to thank the discussers for their kind words and briefly comment on some of the questions raised. We are caught on the horns of a dilemma when using experimental animals. The variability of human subjects has been brought out. If there were a sufficient quantity of humans to do valid statistical studies, and if the doses of methanol the humans get, were accurately known, these things might be eliminated. Using experimental animals, at least these factors can be controlled.

Using experimental animals, one has to sacrifice the direct human application. Using mammals, one knows that most of the cellular metabolism in mam-

mals is identical throughout the class and at least on that basis we feel we are on relatively sound ground.

As far as the visual effects of methanol itself are concerned, it is impossible to comment on the basis of the present work with experimental animals. We are contemplating some electrical studies which may throw more light on this particular subject.

In direct response to the comment about the calculations, we obviously did not mean these calculations to be a hard and fast correlation but simply to indicate orders of magnitude, for even if one multiplied the toxic dose of methanol we used by 10 times, the lethal dose would be right for formaldehyde and not for the other materials. This is not intended to be hard and fast; it is simply corroborative.

In regard to the lack of proportion of blindness with formaldehyde, we have no direct experience on that ourselves and criteria of blindness in experimental animals is something that has bothered us considerably. We can only quote the paper of Flury and Wirth that was published in the early thirties, which stated that the effects of methyl alcohol and the effects of formaldehyde have been shown to be identical in experimental animals.

As far as methyl salicylate is concerned, we have no direct knowledge of the amount of penetration of methyl salicylate into the body. The rate of hydrolysis of such aromatic esters is perhaps not as rapid as some of the lower esters in the body, but when you consider the necessity for skin penetration, it is hard to believe that as much as 10 grams equivalent of methyl alcohol would be likely to be absorbed through the skin.

In reply to Dr. Casten, we should mention that we had been deeply impressed in the past by the paper of Berger and others quoted by him. On the evidence presented by these authors the treatment of acidosis would seem to be an important aspect of the treatment of human methanol poisoning. The work on acidosis reported by previous authors has never been adequately substantiated by chemical determinations.

The acidosis problem is, however, a complicated one.

First, the acidosis must be secondary to some other toxic mechanism since, if all the methanol in a large toxic dose (100 cc.) were converted to a formic acid, the body buffers would be adequate to prevent acidosis. This question of the mechanism of acidosis is now under investigation in our laboratory.

The second point is that acidosis can have no connection with the loss of vision. Other clinical conditions which cause as profound an acidosis, such as diabetic coma, have no effect on vision and do not cause retinal or optic nerve changes. Thus, although treatment to increase alkali reserve is important for the health of the patient it does not bear directly either on the mechanism of methanol toxicity or on the associated visual effects.

DR. ANITA P. GILGER (closing): In answer to Dr. Leinfelder, we were interested in the toxicity of the other agents besides the methanol that we tested. All of our experiments were set up with three groups of animals: one group constituted the methanol control, one group was given the sub-

stance that was being tested, and the third group received both substances in the same dosages as the controls. No experiments reported here were run at dosage levels of the tested substances which were lethal by themselves.

ELECTROPHYSIOLOGIC STUDY OF THE RETINA DURING METABOLIC IMPAIRMENT*

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In the course of a study aimed to analyze the effects of metabolic impairment on nervous functions it happened that, in competition with several other members of the central nervous system, the retina became the most emphatic one. It showed a number of peculiarities when electrical phenomena were employed for the measurement of function while the experimental animal was exposed to procedures known to affect the aerobic and anaerobic metabolism. In the following, the results obtained and the methods used will be outlined inasmuch as they might bear on problems of retinal pathology and clinical electroretinography.

The electrical phenomena utilized in our study are summarized in Figure 1. They are well known these days, thanks to the experimental efforts of Ragnar Granit and his associates.

For the measurement of electrical potentials across the eyeball, an unpolarizable electrode is brought into contact with the cornea while the reference electrode is either placed behind the globe or is attached to any point of the head distinct from the eyes if the first-mentioned procedure is not feasible. To prevent interference by eye movements the animals are narcotized, decerebrated, or immobilized by curare during artificial ventilation.

Such an electrode position will first reveal the presence of a steady potential across the globe in the order of several millivolts (de-

pending on the species) to which has been attached the name "resting potential."

Though known for more than 100 years the origin of this potential is still obscure, chiefly due to the fact that it tends to escape analysis by a rapid decline to insignificant values whenever manipulations of the eyeball or of the retina are involved.

Tracing 2 of Figure 1 indicates, however, an experimental tool which promises to be of help. The tracing referred to shows that rapid intravenous injection of small amounts of sodium azide (NaN_3) produces an instantaneous and transient rise of the resting potential; it does so even in cases in which the resting potential is very low or of slightly reversed polarity.

The present status of our experience with this tool seems to indicate that the resting potential is the outcome of a complex function in which the activity of retinal metabolism and ion-transport processes between retina and extraretinal tissue participate.

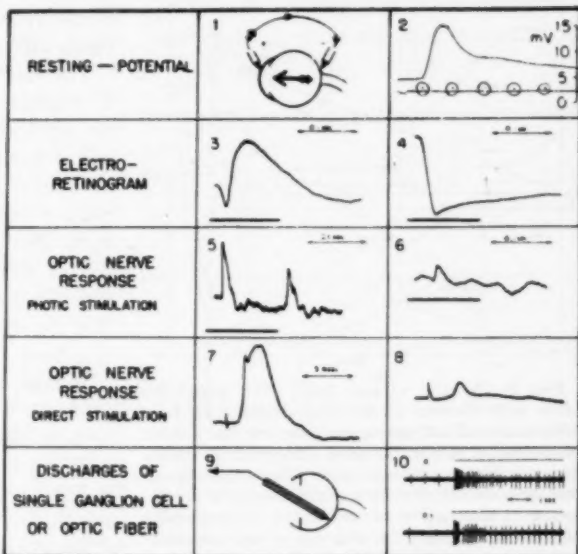
It is felt that a method for the measurement of the resting potential in patients would be a useful addition to the electroretinographic technique. Probably it would suffice to record the potential variations at corresponding points outside the orbit in response to a standardized type of eye movement.

In response to illumination, electrodes across the globe record a sequence of potential changes which conventionally is called the electroretinogram. Tracing 3 of Figure 1 shows a typical oscillographic record of the

* From the U. S. Air Force School of Aviation Medicine.

Fig. 1 (Noell). *The electrical phenomena of the eye.*

(1) Electrode position for the measurement of the potential across the eyeball. (2) The response of the resting potential (rabbit) to parenteral administration of 0.5 mg/kg. of sodium azide. The mark on the lower line indicates that at this point the agent was rapidly injected into an ear-vein. The distance from one dot above the baseline to the next indicates five seconds. (3) Initial portion of a normal electroretinogram (rabbit) in response to a short flash of light indicated by the heavy, horizontal line. (4) Electroretinogram obtained 100 seconds after intravenous administration of iodoacetate. Same amplification as in 3. (5 and 6) Optic-tract potentials simultaneously recorded with the electroretinograms (3, 4). (7) Optic tract potential (rabbit) in response to a maximal electrical stimulus (condensor discharge) to the optic nerve. The small deflection at the left side of the tracing marks the occurrence of the stimulus. (8) Response to some stimulus as in (7) 288 seconds after the induction of anoxia by nitrogen breathing. (9) Schematic drawing of Granit's technique for obtaining discharge from single elements. (10) Responses of an element which in the dark is spontaneously active. During the horizontal line above each tracing the eye is exposed to 0.01 lambert (upper tracing) and 0.1 lambert (lower tracing). The element is the so-called "on-fiber."



initial portion of this response (a- and b-waves). It is written by a single sweep of the cathode-ray beam which is triggered by the light stimulus itself.

As analyzed by Granit the electroretinogram is the sum of three or more component potentials thought to be produced by processes which differ in the site or mechanism of their generation. Tracing 4 serves to demonstrate this fact by a very instructive example.

It is obtained from a rabbit which, 100 seconds previous to the recording of the response, had been poisoned by intravenous administration of iodoacetate, the effects of which will be discussed later in detail. The tracing shows that the disappearance of the b-wave is accompanied by the appearance of a very high and long-lasting a-wave potential which normally is masked by the slightly later developing b-wave.

As has been often emphasized, the decline of the b-wave is associated with a reduction

of the optic-nerve activity in response to illumination. See Figure 1-6. Due to the different nature of both types of activity (b-wave process, optic-nerve discharges) proportionate changes cannot be expected generally. In our experience, the more specifically the b-wave process seems to be disturbed, the later follows the failure of optic-nerve activity.

Since the electroretinogram does not contain a noticeable component which originates from the activity of the ganglion cell layer or the optic nerve, evidence regarding the functional state of the innermost layers of the retina must be obtained by direct experimental approach.

In our routine technique, coarse wire electrodes are inserted into the optic tract midway between chiasma and geniculate ganglion through the skull and brain. Tracings 5 and 6 of Figure 1 show examples of optic-tract potentials obtained by this technique. They were simultaneously recorded with the

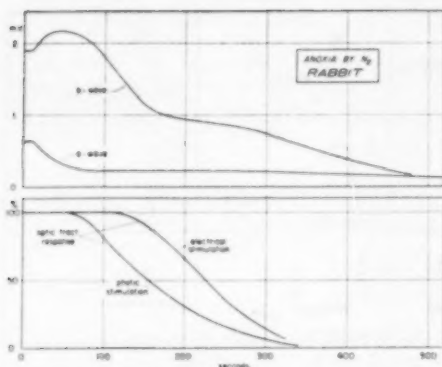


Fig. 2 (Noell). (Upper half) The amplitudes of a- and b-waves of the electroretinogram have been measured and averaged. Note that the a-wave of the rabbit is initially more susceptible to anoxia than the b-wave. (Lower half) The amplitudes of the on-wave of the optic tract potential in response to illumination of the eye and the amplitudes of the tract potential in response to maximal electrical stimulation of the optic nerve have been averaged. Note that both responses seem to disappear at about the same time.

electroretinograms illustrated in the second row.

The two elevations of the normal tracing 5 are caused by the synchronous activity of many optic fibers at the onset and at the cessation of illumination respectively. A decrease of these potentials during purposely induced disturbance of retinal function indicates that the conduction of impulses through the inner layers of the retina has diminished for one of two reasons, either because the ganglion cells receive a reduced number of impulses from the outer layers and the bipolar cells or because the functioning of the ganglion cells or of the optic nerve itself has been impaired.

To facilitate the choice between these two possibilities, the excitability of the optic nerve is tested by direct electrical stimuli through electrodes around the optic nerve shortly behind the globe and the responses being recorded from the optic tract. See Figure 1-7 and 8. The procedure allows measurement in short intervals for the same eye

of the responses of the optic nerve both to photic and to electrical stimulation.

The last step of the experimental procedure intends to obtain information regarding the intricate pattern of retinal discharges (fig. 1-9 and 10). According to the technique of Granit, a micro-electrode is brought into contact with a single ganglion cell or optic nerve fiber at the inner surface of the retina, but, as will be easily understood, numerous experiments of this type are necessary before the effect of any agent can be adequately described.

In man, retinal anoxia or asphyxia rapidly produces what is called "black-out," as can be best demonstrated by the application of centrifugal force to the head or of pressure to the eye, both techniques being effective by a reduction of the intraocular blood flow.

Every experiment, however, performed with a rabbit demonstrates very convincingly that the low resistance of the retina against anoxia, suggested by the human behavior, does not hold true for all mammals. The graphs of Figure 2 will indicate how differently the rabbit's retina seems to behave.

The rabbits, from which these graphs are derived, were exposed to anoxia induced by nitrogen breathing. Cessation of respiration generally occurred within 30 seconds and death within two to three minutes. The optic nerve, however, conducted impulses in response to illumination of the eye for five minutes or more, indicating that, for such a long period of anoxia, all the different structures of the retinal pathway remained at least partially functioning.

At the time of the disappearance of the optic tract potentials, moreover, the b-wave of the electroretinogram was still present, in fact it took about 15 minutes after the death of the animal until the electroretinogram had vanished. In the rabbit, therefore, the disappearance of the optic-nerve activity is not due to the failure of those retinal processes which produce the electroretinogram.

By testing the optic nerve excitability, em-

playing electrical stimuli as indicated in the preceding figure, it was found that, in the rabbit, the anoxic failure of the peripheral portion of the visual pathway must be initiated by inexcitability of the optic nerve and hence of the ganglion cells.¹

To demonstrate the great variations in the anoxic resistance of the vertebrate retina, Figure 4 gives a compilation of data on the failure of the b-wave in various species. Each graph represents the average decline of the amplitude of the b-wave after asphyxia of the eye had been induced.

For a better comparison of man with monkey, cat, and rabbit, asphyxia was produced in these species by the application of high pressure against the eyeball sufficient to block the intraocular blood flow. There are some differences between the effects of high intraocular pressure and of general anoxia (compare figs. 2 and 3 with the corresponding graphs of fig. 4); for the purpose of this comparison they are, however, negligible.

The most surprising result of this comparison is the slow decline of the b-wave in man. After a sharp initial drop in amplitude (which probably is due to a change in the position of the eye with regard to electrodes and light source), the decline of the b-wave follows a course which is similar to that of the rabbit but distinctly different from that of cat and monkey. Total black-out to a strong flash of 100-lambert intensity had oc-

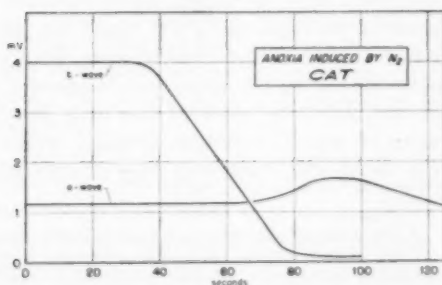


Fig. 3 (Noell). Compare with Figure 2 and note the differences in the anoxic susceptibility of the electroretinogram between rabbit and cat.

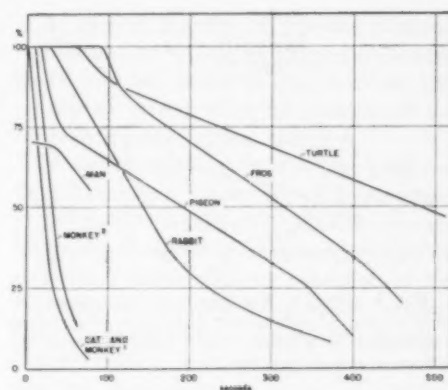


Fig. 4 (Noell). Decline of the b-wave during local asphyxia or general anoxia. In cat, monkey¹ (Macaca mulatta), man, and rabbit, retinal anoxia is produced by an increase of the intraocular pressure sufficient to block intraocular blood circulation. The decline of the b-wave is the same in cat and monkey. The graph labelled monkey² results from an experiment during which anoxia was produced by explosive decompression. Note that after an initial delay (circulation time) the decline of the b-wave follows the same time course as in local asphyxia induced by pressure. The slower decline of the b-wave in frog (*Rana pipiens*) and turtle (*Chelydra serpentina*) than in mammals is largely due to their lower body temperature (24°C.—26°C.). In frog and turtle anoxia is produced by the interruption of the blood supply to the head, in the pigeon by exposure to nitrogen atmosphere.

curred, nevertheless, after about 50 seconds—that is, at a time when the b-wave was still 50 percent of its size before the onset of asphyxia.

These findings allow the conclusion that the black-out in man due to retinal asphyxia is not caused by the failure of those processes which generate the electroretinogram; it then follows that the visual cells at least are functioning when black-out occurs, and that changes within the nervous pathway must be responsible for the disturbance of vision.

Since for the rabbit and cat the experimental findings indicate that the bipolar cells are more resistant to anoxia than the optic nerve,² it seems most likely that, in man, the asphyxial block of impulse propagation is initiated within the ganglion cell neuron.

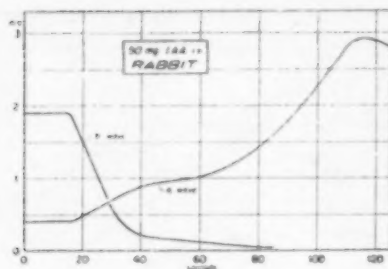


Fig. 5 (Noell). The effect of intravenous administration of iodoacetate (IAA) on the electroretinogram in a rabbit. Note difference with the effects of anoxia (fig. 2).

Incidentally, it follows from the analysis already given that the sparing of a central area of the visual field in acute retinal anoxia cannot be explained by differences in the anoxic resistance of rods and cones.^{3,4} The fact that the b-wave can be evoked when vision has been lost makes such a view untenable.

Most living matter relies on energy derived from aerobic reactions and the rapid effects of anoxia are a fair demonstration of the ineffectiveness of anaerobic processes to support nervous functioning. In comparison with other nervous functions, the retinal processes are neither particularly sensitive nor unusually resistant to anoxia.

The disappearance of the very sensitive b-wave of cat and monkey occurs still later than the cessation of the brain-wave activity in these species. During explosive decompression, vision in man does not vanish before unconsciousness is produced. On the other hand, the long persistence of the electroretinogram in the rabbit is surpassed by the survival time of sympathetic ganglia.⁵

In contrast to other nervous structures, however, the retina of homeothermic animals possesses a great anaerobic activity as indicated by a lactic-acid production which surpasses that of many malignant tumors. We believe that this property is responsible for the finding that iodoacetate is a very powerful retinal poison when injected intravenously.⁶

Iodoacetate is an inhibitor of sulfhydryl enzymes, one of which is the triosephosphate dehydrogenase of glycolysis. In vitro it produces, therefore, inhibition of lactic-acid production while for several reasons respiration might continue unimpaired for a certain length of time particularly if substrates utilizable in the aerobic cycle are supplied. Thus, for instance, lactate and pyruvate have been shown to counteract completely the ef-

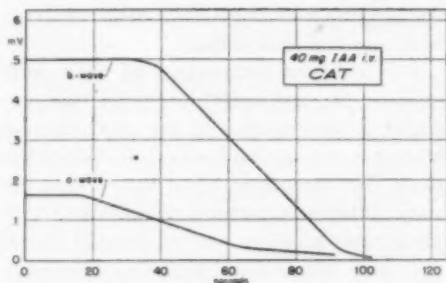


Fig. 6 (Noell). The effect of intravenous administration of iodoacetate (IAA) on the electroretinogram in a cat. Note difference with the effects of anoxia (fig. 3) and also the difference between cat and rabbit (fig. 5).

fects of iodoacetate on the resting potential of isolated frog nerves.⁷

As Figures 5 and 6 show, intravenous injection of iodoacetate produced almost immediate effects on the electroretinogram which were associated with a marked reduction in the size of the optic nerve potentials. Microelectrodes were, therefore, inserted into the layers of the retina and it was found that the retina became almost entirely silent shortly after the electroretinogram had disappeared. It was, therefore, assumed that early processes of retinal excitation, probably within the visual cells, must have been affected by

* The greater resistance of the visual cells near the ora serrata against iodoacetate poisoning (described in one of the following paragraphs) could be due to the utilization of lactic acid which might enter the retina with greater ease by diffusion from the aqueous humor than by passing the blood-retina barrier (see Himwich⁸ for discussion on the lactic-acid permeability of the blood-brain barrier).

the poison.⁶ This conclusion was later verified by a histologic study.

There are several possibilities to explain why iodoacetate has such marked effects on the retina. For instance, Wald and Brown⁹ recently demonstrated that sulfhydryl groups are involved in the binding of carotenoid to protein in rhodopsin and that sulfhydryl reagents are able to block the regeneration of rhodopsin after bleaching by light. Iodoacetate, however, did not have this effect.

Our own efforts to measure the effect of iodoacetate on adaptation processes *in vivo* did not produce conclusive results, except for the finding that the "off"-wave of the optic tract response was preferentially susceptible to iodoacetate. On the other hand, much evidence was gathered in favor of the assumption that iodoacetate produced its effects on retinal functioning by the inhibition of glycolysis.

First, in rabbit and cat, those components of the electroretinogram which resisted anoxia were most susceptible to iodoacetate, whereas, others which were susceptible to anoxia were not immediately affected by the poison (compare fig. 5 with fig. 2 and fig. 6 with fig. 3).

Second, iodoacetate primarily did not affect the same component of the electroretinogram in cat and rabbit (compare figs. 5 and 6) contrary to what should be expected if it inhibited specifically one fundamental reaction of vision.

Third, in winter frogs, iodoacetate was ineffective during aerobic conditions in accordance to *in vitro* findings that in lower vertebrates the aerobic lactic acid production is very small.

The ability of the eye-potentials to recover after one single injection of iodoacetate has brought about their disappearance has not been determined yet, but it was experienced that vision and pupillary reflexes returned in the course of several hours. Permanent blindness was, however, consistently produced with two to three injections of iodoacetate during a 24- or 48-hour period.

(The general toxicity of repeated administration was no serious experimental obstacle in rabbits, but severe central nervous and circulatory effects were encountered in the cat if such procedure was used.)

In the few instances in which we observed the initial stages of recovery after one single injection, the optic-nerve potentials in response to illumination regained appreciable amplitudes earlier than the potentials of the electroretinogram, reminding one of the clinical experience (Karpe, Riggs) that the electroretinogram may have vanished before vision has deteriorated in cases of retinitis pigmentosa.

The conclusions arrived at by the electrophysiologic analysis of the effects of iodoacetate were confirmed by a histopathologic study, which will be reported on in detail elsewhere. It was found that iodoacetate administration resulted in the disappearance of the visual cells.

The degenerative process induced by iodoacetate either involved simultaneously all organelles of the visual cells or it started with the destruction of outer and inner segments, followed by pyknosis of the outer nuclear layer. The process came to a temporary standstill with the disappearance of the outer nuclear layer. The neuro-epithelium near the ora serrata was more resistant than other portions of the visual-cell population and a smaller area around the optic nerve was also often preserved when the outer nuclei had disappeared elsewhere (two to three weeks after the repeated administration of iodoacetate).

In the albino rabbits, the pigment epithelium (sine pigmentation) was variably affected, in the cat clumps of pigment deposits developed ophthalmoscopically and histologically solid nodules of pigment were found within those parts of the retina which were not attached to the tapetum. The retinal vessels of the cat became markedly narrowed.

In short there was a remarkable similarity between the effects of iodoacetate and the

histologic changes in cases of primary degeneration of the neuro-epithelium on a hereditary basis (retinitis pigmentosa).

The confirmation of the results of the electrophysiologic analysis by histologic findings opens the question whether or not the similarity in the effects of iodoacetate and retinitis pigmentosa may shed some light on the nature of the disease. It does so indirectly in suggesting the consideration of a (genetically conditioned) disturbance of the carbohydrate metabolism of the visual cells as a lead for the eventual elucidation of the disease.

Furthermore, due to its primary effect on the visual cells iodoacetate promises to be a tool for the study of various pathogenetic problems of the disease such as those concerning pigment migration, narrowing of retinal vessels, glia reactions, and the early

sparing of the visual cells near the ora serrata.

SUMMARY

1. Over the mammalian scale a remarkable lack in consistency exists with regard to either the energetic demands or the mechanism of energy supply for the various processes of the retina. This lack of uniformity conditions great variations in the anoxic resistance of retinal potentials.

2. In rabbit and cat intravenous administration of iodoacetate produces almost immediate effects on the electroretinogram and optic nerve activity which result in transient or permanent blindness.

3. Repeated iodoacetate administration produces severe histologic changes which are dominated by the disappearance of the neuro-epithelial elements.

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DISCUSSION

DR. JAME E. LEBENSOHN (Chicago): Dr. Noell has given an interesting and detailed analysis of research bearing on the interpretation of the electroretinogram. His first chart on historical development showed the start of our accumulating knowledge with the discovery of the resting potential by Du Bois-Reymond, who is justly credited as the pioneer in electrophysiology. But actually we owe to Benjamin Franklin not only bifocals but the impetus to this field of study.

When Franklin identified lightning and electricity, the renewed interest in electrical phenomena which this discovery occasioned finally resulted in the epochal contributions of Volta and Galvani.

The electrical experiments on the frog fascinated scientists, and Humboldt suggested to Johannes Müller further study of the interrelations between life and electricity. Müller delegated this project to Du Bois-Reymond who, in the finest tradition of Teutonic thoroughness, founded the science of electrophysiology.

The resting potential which Du Bois-Reymond noted has been shown to be based on the same metabolic activity as the active potential later discovered by Holmgren in 1866. Dewar and McKendrick of Scotland observed in 1873 that the invertebrate eye with its erect retina has a resting potential of the opposite sign to that of the ver-

tebrate eye, signifying that the electric response of the eye, at rest as well as in action, is maintained by the visual cells.

Granit's experimental work on the electroretinogram in animals definitely demonstrated that the three processes postulated by Einthoven actually existed. After the use of ether, Processes I, II, and III disappeared in that sequence. He also showed the selective action of other agents such as alcohol, atropine, adrenalin, and potassium chloride.

The experiments of Dr. Noell with two new drugs, iodoacetic acid and sodium azide, emphasize the role of glycolysis in the retina, which has been stressed by the previous speakers in relation to methanol poisoning.

This notable paper is a fitting supplement to the monumental work of Granit, and likewise indicates the great value of the electroretinogram in clarifying our knowledge of the mechanisms of the retina.

DR. WILLIAM J. HOLMES (Honolulu): I believe most of us are more interested in the clinical possibilities of electroretinography rather than basic laboratory studies. Electroretinography from a laboratory research standpoint has been studied by Prof. Ragnar Granit at the Nobel Institute in Stockholm, Sweden. It has also been used exten-

sively for clinical conditions by Dr. Gosta Karpe at the Karolinska Hospital in the same city. Dr. Karpe has amassed a great many representative curves for various diseased conditions of the eye.

Last year, while visiting in Stockholm, I had an opportunity to attend Dr. Karpe's clinic and observe his technique. The technique consists of preliminary dark adaptation of the eyes for 30 minutes. The eye is then anesthetized with pontocaine and a speculum is inserted. The active electrode is placed on the cornea by means of a contact glass filled with saline and a neutral electrode is secured to the forehead by a band. The stimulus consists of a sharp, sometimes painful, exposure of light which varies in intensities from 1 to 5, to 20 to 80 lux.

Dr. Karpe was able to record consistent changes on the electroretinogram of patients with retinal detachments, retained metallic intraocular foreign bodies, circulatory disturbances of the retina and others.

At the time of my visit, the staff was working on a research project involving the electroretinographic researches of newborn babies from birth to six months of age.

I again wish to thank Dr. Noell for bringing this subject before us. It is my feeling that in the future we will hear much more about it.

SURVIVAL TIME OF RETINAL CELLS WHEN DEPRIVED OF THEIR BLOOD SUPPLY BY INCREASED INTRAOCULAR PRESSURE*

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INTRODUCTION

Detailed experimental knowledge is required of the effect of anemia on the survival time of retinal cells to help clarify several clinical entities.

Loss of the retinal blood supply, following closure of the central retinal artery, results in permanent degenerative changes in the retina after a very short time, but the length of time in which treatment might be of some value is still in doubt.

Blindness, following nitrous-oxide anesthesia, has been described. This is thought to

be caused by asphyxia of the retina, but just how long it takes to affect the retina is not known.

A number of cases of amaurosis, following external pressure to the eyeball during anesthesia, have been recorded. The blindness is thought to be caused by anemia of the retina, produced by a combination of a drop in the blood pressure, by spasm, and by the expression of the blood from the eye by the extraocular pressure. It is not known how long it takes before retinal damage results under these conditions.

In neurosurgery, there are times when the surgeon wishes to occlude the ophthalmic artery for a short time (for example, in operations for arteriovenous aneurysms). It

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would be valuable to know how long circulation could be obstructed without danger to the retina.

In experimental studies to date, difficulties were encountered due to a difference between the arterial supply of the retina of certain animals and that of man. For example, cutting the central retinal artery of the rabbit does not produce degeneration of the retina. This was shown by Wagenmann. On the other hand, Turnbull showed that the same procedure in rats led to a degeneration of the retina similar to that which follows retinal artery occlusion in man.

In a further study, Turnbull produced temporary anemia of the retina by centrifuging rats. Three minutes were sufficient to cause a progressive loss of ganglion cells in the 21 days after the treatment. His technique did not permit him to pursue the problem further, because centrifuging the rats for more than three minutes killed them.

We made use of a technique which permitted us to vary the anemia period from minutes to hours, confined the experimental procedure to the eye alone, and also allowed for a control.

TECHNIQUE

All experiments were performed on rats. Two techniques were used to produce retinal anemia. In the first, the central retinal artery and the long and short ciliary vessels were cut—the purpose being to establish a control for complete retinal anemia.

The second method consisted of increasing the intraocular pressure by introducing sterile fluid into the eye, under sufficient pressure to express all the blood. The pressure was controlled and maintained at a constant level of 100 mm. Hg by using a pressure bottle connected to a mercury manometer. The retinas were studied immediately following these procedures and at selected time intervals thereafter.

RESULTS

In the first group, in which anemia was

produced by cutting the retinal and choroidal vessels, the degenerative changes were first noted in the bipolar cells after 15 to 20 minutes. There was swelling of the nuclei, with a breakdown of the chromatin network. As degeneration progressed, the nuclei shrank and took on a deeply stained, homogeneous appearance. Great variation as to the degree of degeneration was noted from cell to cell—normal cells lying beside cells which were grossly altered. These pyknotic nuclei became progressively more numerous, so that, in four hours, all of the nuclei showed these changes.

The ganglion cells showed degenerative changes as early as 20 to 30 minutes. These changes, however, were quite irregular and indefinite. The occasional cell showed swelling, followed by loss of Nissl's substance and the migration of the nucleus to the periphery of the cell.

The rods and cones showed some loss of differentiation in staining between the inner and outer segments after approximately 20 to 30 minutes. The degenerative process progressed at such a rate that, within six hours, the rods and cones did not show up in the stained preparations.

In the second group in which anemia was produced by expressing the blood from the eye by increased intraocular pressure, the results observed closely paralleled those of Group 1—both as to rate and to type of degeneration. At the end of three hours of anemia, the findings of both methods were almost identical.

If the anemia was for 10 minutes or less, the retina was normal even after 21 days. Following 20 minutes of anemia, after 21 days most of the ganglion and bipolar cells degenerated and were absorbed. If the anemia lasted for more than 30 minutes, after 21 days the retina proceeded to degenerate completely and was reduced to a thin layer of irregularly arranged cells.

DISCUSSION

If the findings in the rat apply to man, the

nerve cells of the retina are injured by anemia if it lasts more than 15 minutes.

The nerve cells are not, however, uniformly sensitive. Changes become visible in the bipolar cells in 15 minutes, in the ganglion cells in 25 to 30 minutes, and in the cell bodies of the rods and cones in 40 to 50 minutes.

Our observation that more than 15 minutes of anemia is necessary to produce degeneration does not agree with that of Turnbull. He found the critical time to be three minutes. It must be pointed out, however, that his technique produced anemia in both eyes and thus deprived him of an adequate control for the assessment of cell damage and cell loss. Furthermore, degeneration in the retina that follows centrifuging may not be

due to the temporary anemia, but to a systemic effect of the treatment which secondarily affected the retina.

It is of interest that the longer survival time of 15 minutes, which we obtained, is comparable to that of the nerve cells of the cerebral cortex which also show no histologic changes after less than 15 minutes of anemia. Gomez and Pike showed this in cats by ligating the cerebral arteries and Becker and Windle in fetal guinea pigs by pinching the umbilical cord.

This work is being continued to verify the above findings and to obtain more detailed information concerning the processes of repair which may follow anemia of short duration.

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DISCUSSION

DR. DERRICK VAIL (Chicago): Before taking up the discussion, I should like to compliment the officers of this society for their new idea of asking clinicians to discuss experimental papers, and I should like to see the Section on Ophthalmology do the same thing by putting the experimental research workers on the spot extemporaneously. It might be interesting to see how the problem is handled.

As the chairman has announced, all of these clinicians have had no warning about the work that they are to discuss and I think that up to the present time they have acquitted themselves very well, and I exclude myself from that category.

I am very much interested in the paper we have just heard because I think it gets to many fundamental clinical problems which have worried all of us. The matter of time in which the retina is deprived of its blood supply before it loses its function has great clinical significance, as the essayist has pointed out in citing a number of clinical instances.

There is one further clinical condition seemingly common, of course, and that is glaucoma. Recently in the literature there has been an increasing number of papers having to do with the problem of glaucoma approached from a vascular angle rather than from that of increased formation of aqueous on the one hand, or decreased outflow of aqueous on the other.

The problem of the field defect that is so commonly seen, especially the early changes in glaucoma explained on the pure basis of pressure on the nerve fibers of the retina, is one that has worried me for a considerable time. I think the solution is much more apt to be on a vascular basis rather than that of a purely pressure phenomenon; in other words, a discontinuance of blood supply to the periphery of the retina over a long period of time, a chronic ischemia produced in elderly people whose blood vessels are already sclerotic, would explain the baring of the blindspot, for example, and the later changes involving the nasal field of vision much more readily than that of pure

pressure on the optic nerve fibers at the disc level.

It would also explain to me some of these cases of so-called low-tension glaucoma where the field defect is exactly comparable to that seen in the ordinary glaucoma, and yet the pressure is not elevated. This syndrome has been known as the carotid sclerosis syndrome described a number of years ago by Knapp and others, whereby the ophthalmic artery receives less than its normal supply of blood through a calcareous type of carotid artery.

All of us have seen cases of glaucoma in which the intraocular pressure has become stabilized and yet the field defects continue, and I think this can be explained only on the basis of constricted blood supply, continuous constricted blood supply, as the result of arteriosclerosis or other changes in the already affected vessels.

These are just a few of the things that passed through my mind when the essayists were discussing the problem. I think that the preceding paper by Dr. Noell can be correlated to some extent with the one we have just heard and I will listen to further discussions and will look into the literature for further solutions of these knotty clinical problems.

DR. P. ROBB McDONALD (Philadelphia): I am sure we have all seen cases in clinical practice in which we have had a partial occlusion of the vessels and have been able to relieve the occlusion with return in function of the retina. We also have cases in which the vessels appear normal but there is a field defect and we have felt that the loss of function must have been due to occlusion of a vessel or temporary spasm.

In the experiment that the authors conducted of increasing intraocular pressure, I presume that that pressure was increased rapidly from whatever the level is in a rat to 100 mm. Hg. We are aware clinically that one can have a patient with edema of the cornea and all the evidences of acute congestive glaucoma but a tension of 40 or 50 mm. Hg, whereas we have seen patients with pressures of 80 and 90 mm. Hg with a perfectly clear cornea. I am sure that in edema of the cornea, as in cases of papilledema, it depends upon how rapidly you increase the pressure in the eye or in the cranial cavity.

I think that if the pressure had been gradually increased in these animals over a longer period of time, you probably would not have had the degeneration and destruction of the retina that was observed.

I agree with Dr. Vail that a lot of the field changes we see in glaucoma are on a vascular basis.

I do not think they are necessarily due to increased pressure.

DR. ARTHUR ALEXANDER KNAPP (New York): It may be interesting to mention that I have had three patients in practice who have come to me three days after being totally blind. On examination the tension was over 90 mm. Hg. A drainage operation was done in all three and today they are seeing. Two of them also are suffering from advanced retinitis pigmentosa, and the vision in one is 20/70 plus, in the second 20/200, and in the third 20/200 minus.

I think that it is interesting to note that, while clinically and experimentally you may feel that blindness, either due to glaucoma or optic-nerve atrophy, is final and irreversible, still there is hope clinically and that surprisingly enough patients can recover vision. We still do not know when clinical and histologic loss of vision coincide. We still do not know the potential vision of clinically blind eyes.

DR. HENRI PICHETTE (Quebec City, Canada): We certainly need more fundamental data on the ocular circulation. The slowness of the blood flow, as well as the complete blockade of the blood supply, always produces slight or severe anemia or ischemia in the retinal cells.

In the same manner, the lack of permeability of the arteriolar wall and cellular plasma membrane will bring about important histologic changes in the ocular layers.

Besides the factor of permeability itself, there may intervene other factors, such as the number and size of the transversing molecules and chylomicrons in the lymph and blood systems. This last point was stressed a few months ago by Moreton. Oversized particles and macromolecules can very easily block the microcapillaries and produce ischemia or local thrombosis. These facts enable us better to understand the very complex phenomenology of the retinal disturbances.

DR. C. D. BAIRD (closing): In answer to Dr. McDonald, we are working with a time factor here and, therefore, to get any accurate results we had to increase our pressure rapidly. Otherwise, our time factor would have had very little meaning.

Dr. Knapp speaks of the occlusion of veins in the central area of the retina, but we must remember in his case the choroidal vessels were still giving a certain amount of nutrition to the retina, which would possibly account for the fact that these people were able to maintain some vision after a great deal longer time than 15 minutes.

THE ANTERIOR CHAMBER OF THE EYE FOR INVESTIGATIVE PURPOSES*

A SITE FOR TRANSPLANTATION OF FETAL ENDOCRINE TISSUES AND CANCER, AND FOR THE STUDY OF TISSUE REACTION

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The purpose of this paper is to point out certain uses to which the anterior chamber of the eye is particularly adapted for the investigation of various problems which are not necessarily ophthalmic. During the past two years, in the Surgical Research Laboratory of the Buffalo General Hospital, the anterior chamber of the eye has been used in the study of: (1) Tissue reaction to foreign materials; (2) the homologous transplantation of fetal endocrine tissue in adult nonrelated hosts; and (3) the heterologous transplantation of human cancer.

I. ANTERIOR CHAMBER IN STUDY OF TISSUE REACTION TO FOREIGN MATERIAL

Since the time of Cohnheim, studies of this nature have used the classical and standard histologic techniques for the study of sterile inflammation. In certain instances, such a laborious and time-consuming procedure is unnecessary if one elects to use the anterior chamber of the eye. By using this method, one may observe the eye daily for tissue reaction.

Figure 1 demonstrates a small piece of polyethylene tubing inserted into the anterior

chamber of a rabbit's eye some three months previously. This piece of tubing was brought to our laboratory by a member of the department of anesthesia who wished to know if the tubing was reactive. The anesthetist wished to place the tubing within the spinal epidural space in order to give analgesia, over a period of several weeks, to a patient with an inoperable and painful carcinoma. If the anesthetist has at his disposal non-reactive tubing, he may, in selected cases, spare the patient a cordotomy for the relief of intractable pain.

One will note from Figure 1 that, as far as tissue reaction is concerned, there is little,



Fig. 1 (Dameron). Rabbit with test sample of polyethylene tubing placed in the anterior chamber of the eye for over three months. Demonstrates minimal tissue reaction.

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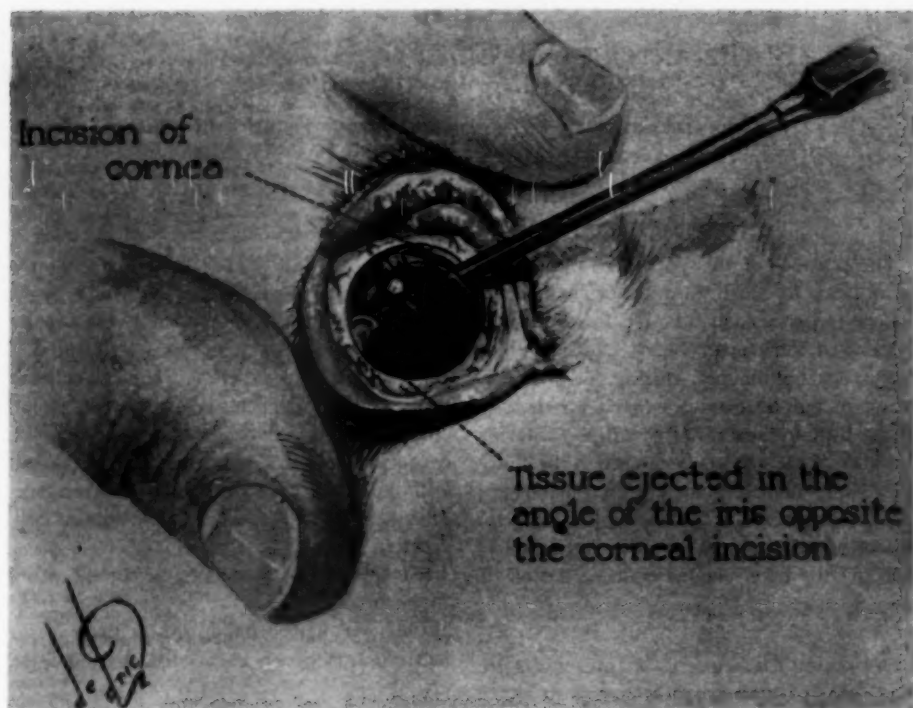


Fig. 2 (Dameron). Illustration of the method of transplanting fetal endocrine tissue or cancer to the anterior chamber of the eye.

if any. The piece of tubing may be used with safety, as far as tissue reaction is concerned, over a period of several weeks.

The orthopedists are still looking for the perfect nonreactive metal for the plating of bones, the nailing of hips, and so on. It might well be that such a method of observing the tissue reaction to metals would be of value to the orthopedists; it also offers a method of observing the tissue reaction to various suture materials.

After the initial reaction to the corneal incision is over, the eye will continue to show signs of progressive tissue reaction if the foreign material is reactive but will clear entirely if tissue reaction is minimal. Thus the enormous amount of histologic study which is now necessary for such an investigation may be saved.

2. HOMOLOGOUS TRANSPLANTATION OF FETAL ENDOCRINE TISSUES TO ADULT NONRELATED HOSTS

Early embryonic tissues have apparently not developed tissue specificity. In other words, fetal tissues possess autonomy and may be transplanted homologously to the anterior chamber of the eye, with indefinite survival. Fetal transplants of adrenal, ovary, testes, and thyroid tissue have been made in the dog, guinea pig, and rabbit.¹

METHOD

The fetuses are removed aseptically by cesarean section and, with the aid of a dissecting microscope, the endocrine tissues are removed and placed in a sterile Petri dish. The bottom of the dish contains a few drops

of the mother's blood, which will furnish sufficient serum to keep the tissues moist until transplanted. Drying of the tiny tissue fragments, and sepsis, are the two greatest deterrents to successful transplantation of endocrine tissues. The endocrine tissues for transplantation are removed between the 19th and 22nd day of gestation in the rabbit and between the 30th and 42nd day in the dog and guinea pig.

The eye of the host is anesthetized with either seven-percent cocaine or one-percent pontocaine. Figure 2 is a drawing that shows a small incision along the upper border of the corneoscleral junction which is made by a quick jab of a corneal knife. Sufficient fluid is allowed to escape in order partially to collapse the anterior chamber.

The tissue to be transplanted is placed within a small sterile trochar and the trochar is then inserted into the anterior chamber. The tissue is ejected from the trochar by a stilette into the inferior angle of the iris opposite the corneal incision. The fragment of tissue, measuring two to three mm. in diameter, is guided farther down into the junction of the iris and conjunctiva by external pressure on the cornea. It is not necessary to close the corneal incision.

Postoperative care is usually not necessary. However, if the eye becomes encrusted, this should be removed by simple irrigation with tap water in order to avoid infection. The use of chemotherapy and antibiotics for the control of infection is not necessary, and should not be employed as a substitute for asepsis.

There is always an initial corneal reaction to the stab wound and to the slight trauma which is necessary in guiding the tissue fragment into the inferior angle of the iris. The operative procedure may cause slight hemorrhage. However, within 10 to 15 days the cornea has, as a rule, cleared sufficiently to permit examination of the transplant. By this time the transplant has a pink color which is indicative of survival.

When examined with the low power of a

stereoscopic microscope, an invasion of the transplant with tiny capillaries may be observed, the invading capillaries being derived from the iris. Between the third and fourth weeks, larger invading vessels may be observed with the naked eye.

A transplant which does not survive has a pearl-white appearance resembling thick fibrous tissue. The dead transplant may either be absorbed or remain to become encapsulated and replaced by fibrous tissue. Microscopically the reaction and absorption is a lymphocytic infiltration followed by fibroblastic proliferation and replacement by fibrocytes. Polymorphonuclear leukocytes are seldom observed invading the transplants. No transplant has been recorded as a "take" unless there was histologic evidence of growth and maturation for longer than 30 days. If regression is going to occur, it is usually apparent before 30 days.

Criteria of a "take" are as follows:

At the time of transplantation a control fetal gland, from the same litter of fetuses, is fixed for histologic study, the size and cellular maturity of the fetal endocrine organ being noted. The transplant when removed at a later date is compared with the control section for cellular differentiation into an adult gland and for size. No transplant has been classified as a "take" unless there has been continued growth and cellular differentiation for 30 days or longer. This arbitrary time limit has been set since Leo Leob found most of his homologous transplants regressed at the end of three weeks.⁶

RESULTS

Transplants have been made in over 230 rabbits, 170 guinea pigs, and 53 dogs. One may obtain a 50- to 60-percent survival and continuous growth in the homologous embryonic transplants of adrenal, ovary, testes, and thyroid tissue in adult normal guinea pigs and rabbits. In the dog, the anterior chamber is very large, which allows many of the transplants to float to the center of the

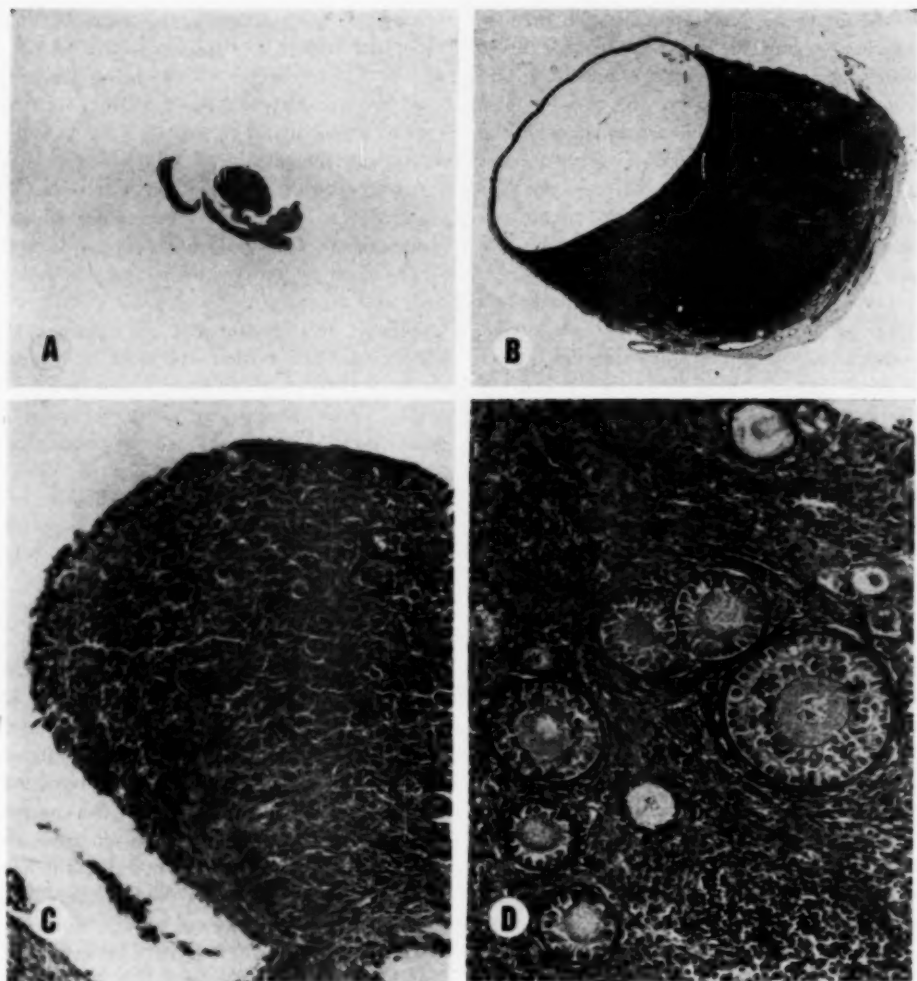


Fig. 3 (Dameron). (A) Section of control fetal ovary, approximately 20th day of gestation. (B) *Rabbit 80*. Identical fetal ovary 66 days after homologous transplantation to the anterior chamber of the eye. Note increase in size, the development of an ovarian cyst, and the mature follicles. (C) Higher magnification of (A), demonstrating immature fetal development of the ovary. (D) Higher magnification of (B), demonstrating the developing follicles in greater detail. (Hematoxylin and triosin.)

cornea, where they die because of lack of blood supply. Therefore, the percentage of "takes" is less in the dog.

In castrated and thyroidectomized hosts, the percentage of "takes" of the ovaries and testes and the thyroid may be increased from 60 percent to approximately 90 percent.

This observation indicates that Halsted's law of endocrine deficiency² is valid and will be reported in greater detail in another communication.

The transplant which survives will increase its volume 300 to over 1,000 times the original volume. There is cellular maturity

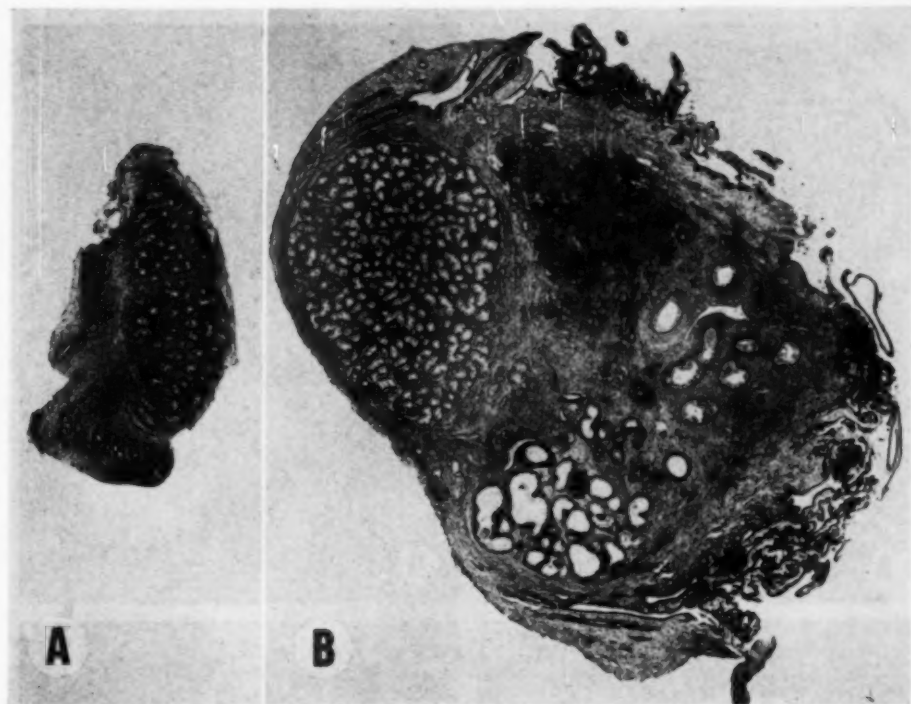


Fig. 4 (Dameron). (A) Section of control fetal rabbit testes, 20th day of gestation. (B) Rabbit 77. Identical testes removed 49 days after transplantation. (Hematoxylin and triosin.)

and differentiation from the fetal form to the adult form.

Ovaries. The fetal transplants when removed 60 to 180 days after transplantation show mature Graafian follicles (fig. 3). In the rabbit, the ovarian transplant at this time will yield a positive Friedman test if the animal is injected intravenously with pregnant urine. Cysts are often formed. The histogenesis of these ovarian cysts is under further investigation.

Testes. There is development of all portions of the testes toward an adult form. Spermatids have been observed in the rete testes (figs. 4 and 5). Spermatozoa have not been observed.

Adrenal. The best growths occur in those hosts who have had a unilateral adrenalectomy; the transplant grows faster and its vol-

ume is greater (fig. 6). There is cellular differentiation into all three zones of the adrenal cortex (fig. 7). The adrenal medulla does not survive.

Thyroid. In the fetal thyroid the follicles are tiny, immature, and rarely possess colloid. The transplant removed 60 days to over one year later is fully developed. The follicles are lined with low cuboidal epithelium and there is an abundance of colloid present (fig. 8).

Dr. John B. Hursh, of the Division of Radiology and Biophysics of the University of Rochester School of Medicine, gave us invaluable aid in obtaining additional evidence that the thyroid transplant functions.

If the animal is injected with radioactive iodine I_{131} , the transplant will take up the iodine to the same degree as the host's nor-

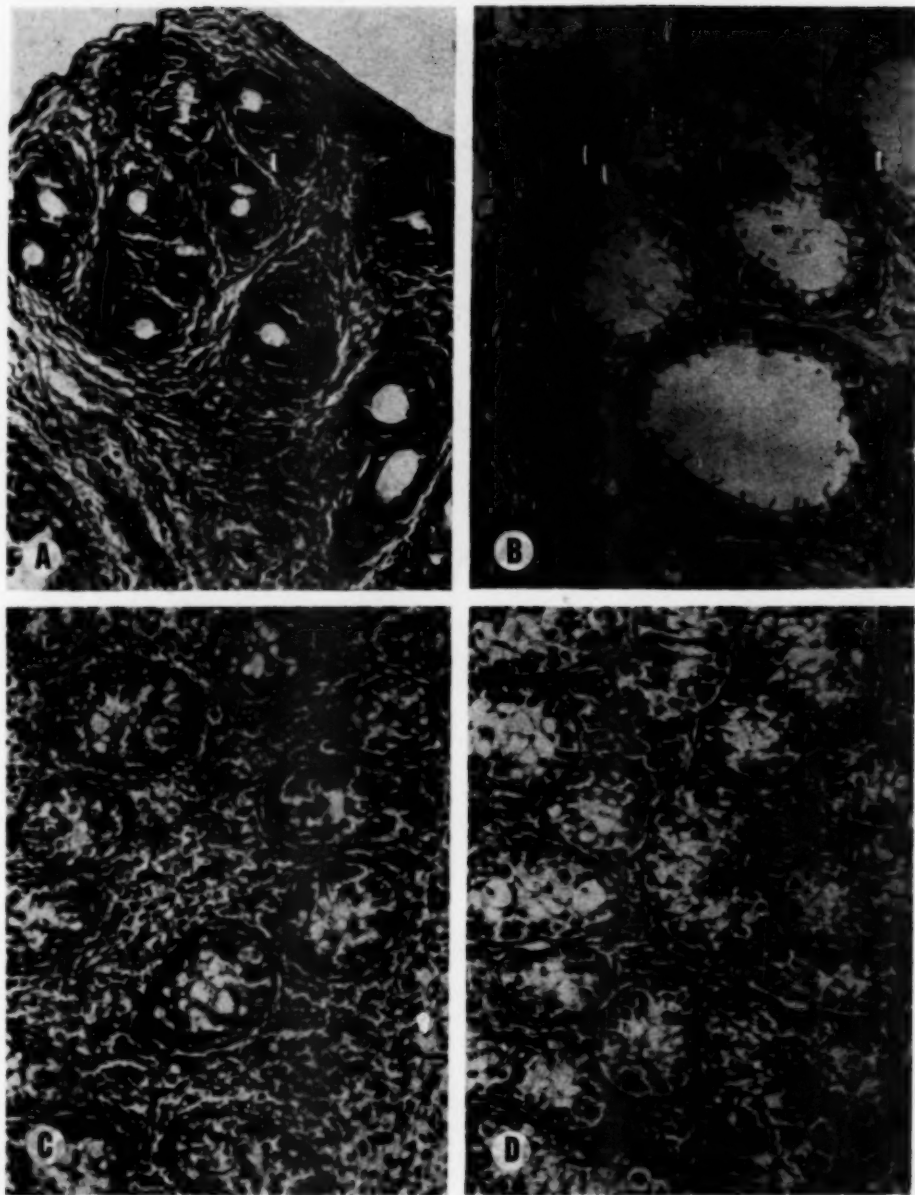


Fig. 5 (Dameron). (A) Higher magnification of Figure 4-A, to demonstrate the cellular detail of the rete testis in the control section. (B) Higher power magnification of the rete testis of the transplant (fig. 4-B), demonstrating spermatid formation. (C) Higher power magnification of the seminiferous tubules of fetal testes. (D) Same magnification of seminiferous tubules of the transplant, demonstrating increased maturation. (Hematoxylin and triosin.)

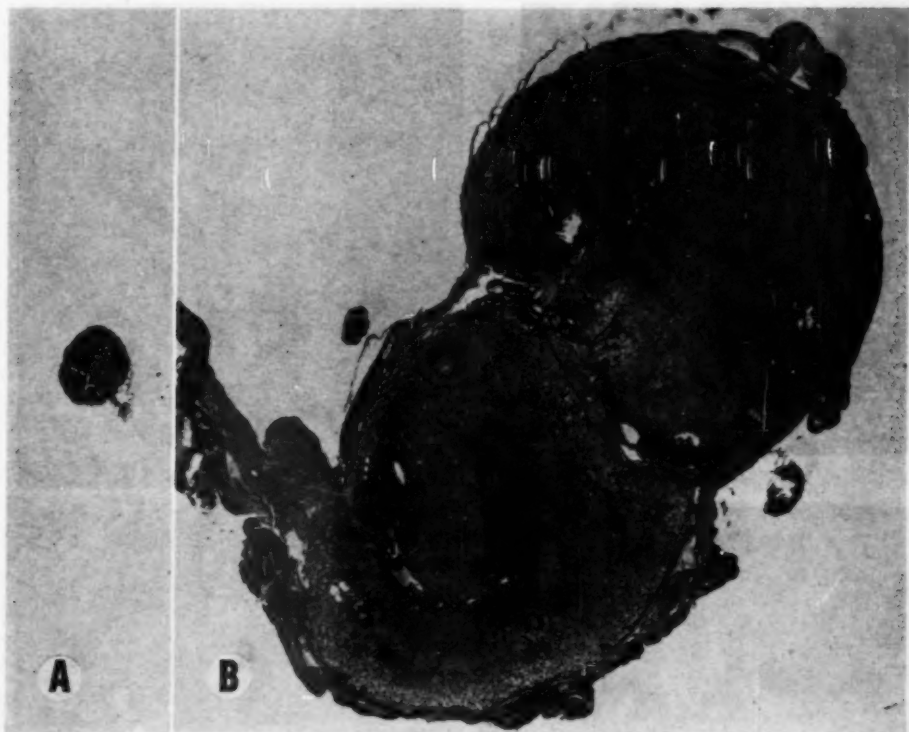


Fig. 6 (Dameron). (A) Control fetal rabbit adrenal tissue, 20th day of gestation. (B) Transplant removed after 112 days. There has been a volume increase of over 1,000 times. The cortex has differentiated into three zones. (Hematoxylin and triosin.)

mal thyroid tissue. In the thyroidectomized host, the transplant will convert inorganic I_{131} to bound-iodine, indicating that the iodine has been incorporated into the thyroxine molecule.

Figure 9 is an autoradiograph of a thyroid transplant injected with I_{131} 24 hours before the autograph was made. There is an abundance of radioactive iodine concentrated within the transplant.

Figure 10 is a photograph of a fetal rabbit thyroid transplant which had been growing for over six months. In our laboratory, guinea pigs have been kept for over one year with transplants. This time represents almost one-half the expected life span of the guinea pig.

These observations indicate that fetal endocrine transplants of adrenal, ovary, testes, and thyroid tissue grow, differentiate from fetal to adult form, and function within the host. Other sites for transplantation besides the anterior chamber of the eye are being investigated in our laboratory in order to obtain a method of transplanting endocrine tissues clinically to deficient patients.

3. TRANSPLANTATION OF HUMAN MALIGNANT TISSUES

Greene^{3,4} has demonstrated on numerous occasions that human cancer may be heterologously transplanted. The ability to transplant human cancer to laboratory animals by Greene's method offers the investigator, for

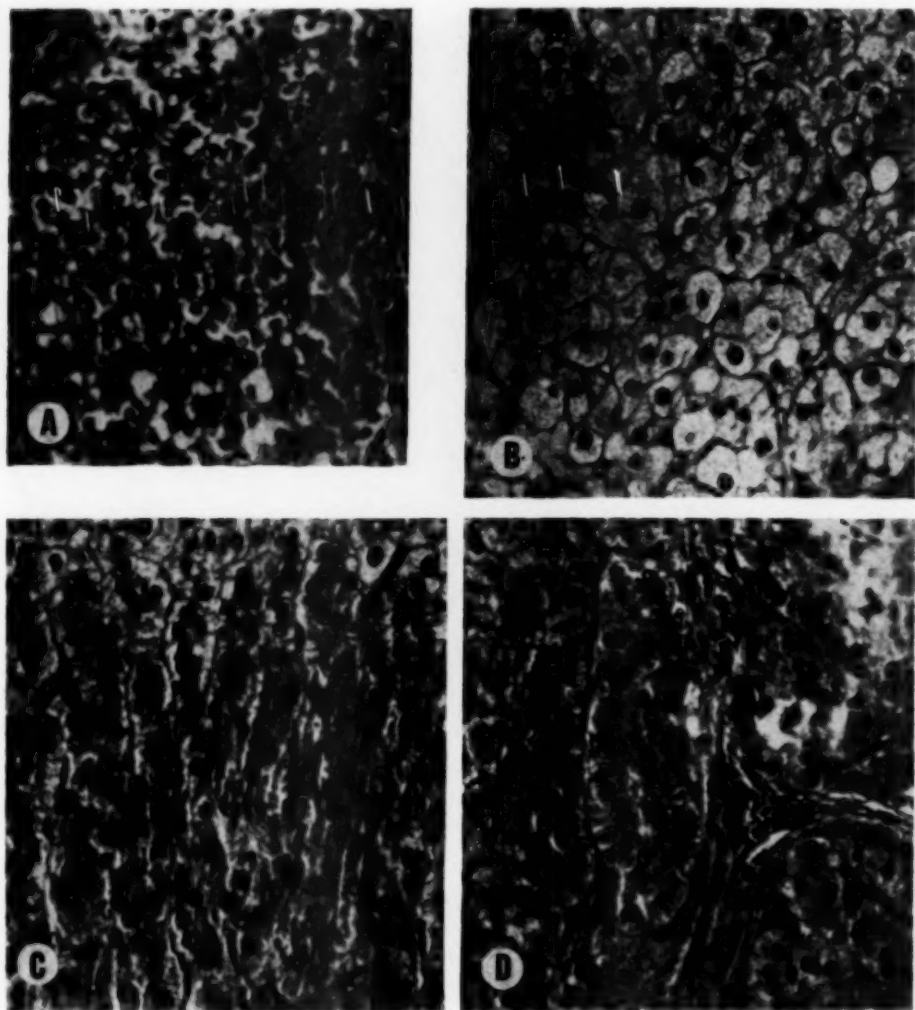


Fig. 7 (Dameron). Higher power magnification of Figure 6. (A) Control fetal adrenal tissue, demonstrating lack of differentiation and organization. (B) Demonstrating the development of broad, flattened cells of the zona glomerulosa of the transplant. (C) Demonstrating development of zona fasciculata of the transplant. (D) Demonstrating development of the zona reticularis of transplant. (Hematoxylin and tricosin.)

the first time, a method of studying human cancer in living laboratory animals. He has introduced a biologic concept to differentiate the malignant from nonmalignant tissues as contrasted against a purely morphologic classification.⁵ For example, the lymphomas and

blood dyscrasias do not grow when transplanted to animals. Neither do all tumors which are classified on a morphologic basis as being cancer grow when transplanted to animals. This has led Greene to question such tumors as being true cancers.

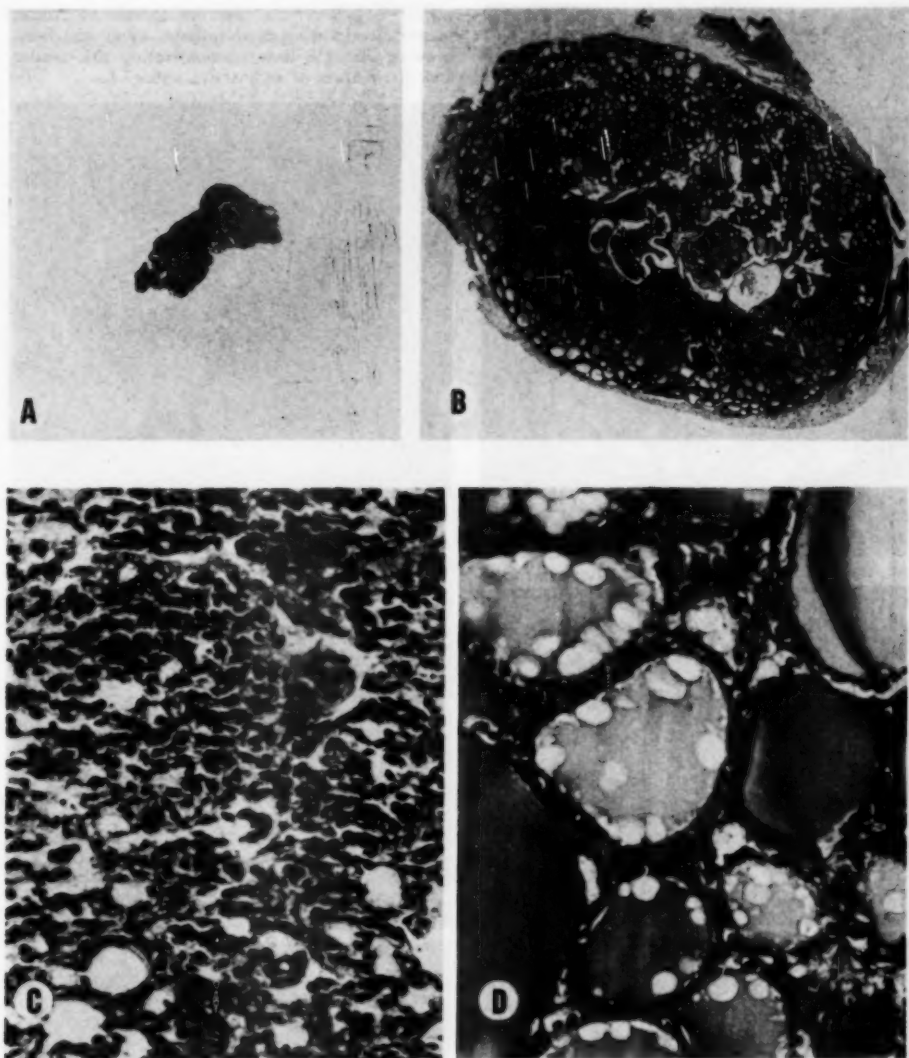


Fig. 8 (Dameron). (A) Control fetal rabbit thyroid tissue, 20th day of gestation. (B) Transplant removed 112 days after transplantation, demonstrating tremendous increase in size and maturation. (C) Higher power magnification of (A), demonstrating the immature follicles and lack of colloid. (D) Higher power magnification of (B), demonstrating mature follicles lined with low cuboidal epithelium and an abundance of colloid. (Hematoxylin and triosin.)

The purpose of this paper is not to go into a lengthy discussion of the merits of the microscope versus the laboratory animal in the differentiation of cancer, but to reemphasize the fact that human cancer may be

studied in laboratory animals. For example, the susceptibility of human malignant tissue to drugs, hormones, or radiation therapy may be advantageously studied in such a manner. Figure 11-A and C is an example of two

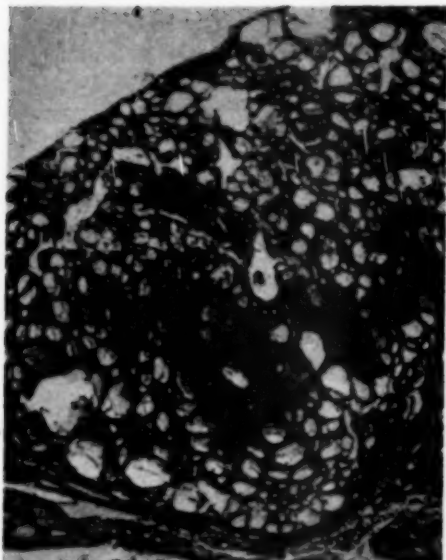


Fig. 9 (Dameron). Autoradiograph of transplanted fetal rabbit thyroid tissue which had been growing for 112 days, demonstrating the uptake and distribution of radioactive iodine, I_{131} .



Fig. 10 (Dameron). Fetal thyroid transplant growing in the eye of a rabbit for over six months.

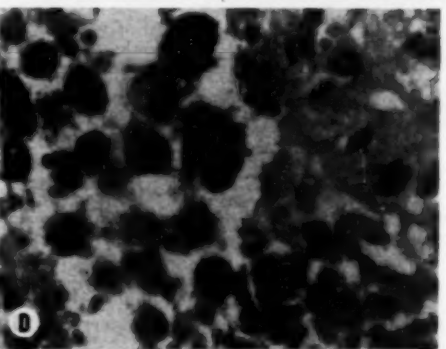
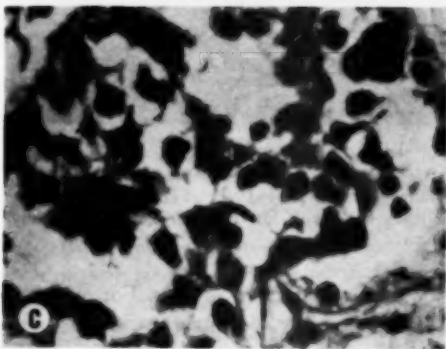
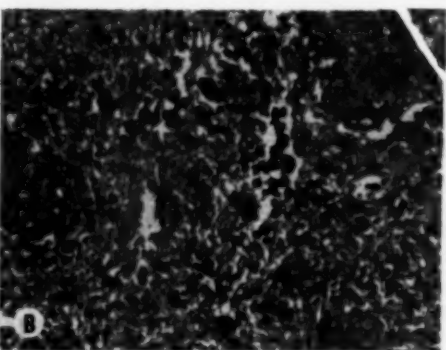
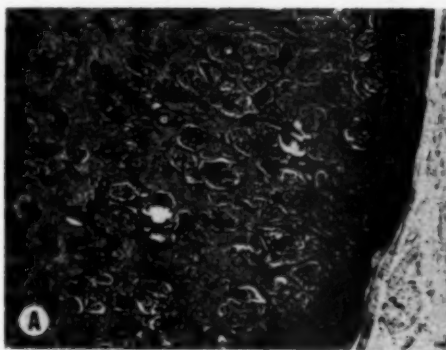


Fig. 11 (Dameron). (A) Transplant of a human papillary medullary thyroid carcinoma to the anterior chamber of a guinea-pig eye. (B) Higher power magnification of (A) to show the malignant cells. (C) Transplant of a human malignant melanoma to the anterior chamber of a rabbit's eye. (D) Higher power magnification of (C) to demonstrate the melanotic cells. (Hematoxylin and triosin.)

human cancers which have been transplanted to the guinea pig and rabbit in our laboratory.

The thyroid carcinoma was obtained* at the time of a lymph-node dissection of the neck. A piece of the cancer was obtained and transplanted to the guinea pig. The cancer grew in the anterior chamber of the eye and was histologically identical to that obtained from the patient. The literature does not reveal a carcinoma of the thyroid as having been transplanted previously.

The malignant melanoma was obtained† at the time of operation and was transplanted within two hours to the anterior chamber of the rabbit's eye. The tumor grew and was histologically identical to the original tumor.

* From a patient of Dr. Roswell Brown.

† From a patient of Dr. Winfield Butsch.

I wish to express appreciation to Dr. John R. Paine, chairman of the Department of Surgery of the University of Buffalo School of Medicine, for his guidance in this investigative work; to Mr. M. D. Dedrick, of the Department of Medical Illustration, for the illustration and assistance in making the photomicrographs; and to Miss Marjorie W. Egan for technical assistance.

SUMMARY

The anterior chamber of the eye is particularly adapted for carrying out many investigative processes.

1. A simple method of studying the tissue reaction to foreign bodies has been demonstrated. This method does not require histologic techniques. The reaction of the tissues to the foreign body may be observed continuously.

2. Early embryonic endocrine tissues, adrenal, ovary, testes, and thyroid, may be transplanted to adult nonrelated hosts. The transplants continue to grow, differentiate, function, and mature into adult glands. From the evidence presented, transplants are believed to function.

3. The advantages of using the anterior chamber of the eye for the transplantation, biologic differentiation of malignant and nonmalignant tissues, and as a method for the study of human cancer has been emphasized. The successful transplantation of a human thyroid cancer to the guinea pig and the transplantation of a human malignant melanoma have been presented.

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TWENTIETH MEETING
of the
Association for Research in Ophthalmology, Inc.

Proceedings

Business Session
Auditors' Report

Directory of Members
Geographical List

New Members

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Atlantic City, New Jersey
June 13 and 14, 1951

BUSINESS MEETING

Wednesday Afternoon, June 13, 1951

The business session of the Association for Research in Ophthalmology, Inc., convened at 2:00 o'clock in the meeting room of the Malborough-Blenheim Hotel, Atlantic City, New Jersey, with Dr. Kenneth C. Swan presiding.

DR. KENNETH C. SWAN (chairman): The first order of business will be the report of the treasurer, Dr. James H. Allen.

DR. JAMES H. ALLEN: See auditor's report.

DR. KENNETH C. SWAN: The next report will be that of the nominating committee, of which Dr. John McGavic is chairman. In his absence, Dr. John Harris will present the report.

DR. JOHN HARRIS: Mr. Chairman, members of the association: I wish to submit the report of the nominating committee. It is the desire of the nominating committee to submit to the association in nomination for membership on the Board of Trustees, the name of Dr. T. E. Sanders of St. Louis, and to submit to the association the name of Dr. James H. Allen in nomination for reelection as secretary-treasurer.

(It was moved by Dr. Harold Falls and regularly seconded that the report of the nominating committee be accepted.)

DR. KENNETH C. SWAN: It has been moved and seconded that the report of the nominating committee be approved. Therefore, Dr. Sanders will be the new member of the Board of Trustees and our secretary-treasurer will remain in office.

The next report is that of the invitation committee for the International Congress. In the absence of the chairman, Dr. Brittain F. Payne, I will ask Dr. Allen to submit the report.

DR. JAMES H. ALLEN: The invitation committee for the International Congress, consisting of Dr. Brittain Payne, Dr. Phillips Thygeson, and myself, met with the representatives of the three other eye societies and received the report from the executive group of the invitation committee to the effect that the International Congress of Ophthalmology had accepted their invitation to meet in this country in

1954. At that meeting, an organization for the handling of the business and arrangements for the International Congress was formed. Dr. Bernard Samuels was elected president of the International Congress, Dr. John H. Dunnington, vice-president, Dr. William L. Benedict, executive secretary and treasurer.

The matter of advertising and financing the arrangements for the International Congress was discussed and the Association for Research in Ophthalmology, through its committee, with the approval of the Board of Trustees, pledged an initial sum of \$500 to the support of this organization.

This, Mr. President, concludes the report of the invitation committee, and it requests that it be dismissed at this time.

DR. SWAN: Is there any discussion? The chair will receive a motion.

(Upon motion made by Dr. Falls, seconded, and carried, the report of the committee was received.)

DR. SWAN: The Board of Trustees have voted that, in the future, all papers should be submitted in final form at the beginning of the meeting.

The trustees also agreed that presentation of the papers in summary would be acceptable and that we would accept for publication more complete material than was presented at the meeting.

Dr. McDonald, could you now present the report of the auditing committee?

DR. ROBB McDONALD: I have examined the books of the society, the financial statement prepared by an exceptionally good firm of auditors, and, as far as I can tell, they are in good order.

DR. SWAN: May I have a motion that the treasurer's report and the auditor's report be accepted?

(Upon motion regularly made, seconded, and carried, the auditor's report was accepted, carrying with it acceptance of the treasurer's report.)

DR. SWAN: Is there any new business?

If not, we will proceed with the afternoon program.

AUDITOR'S REPORT

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

To the Members of the Board of Trustees
Association for Research in Ophthalmology, Inc.
New Orleans, Louisiana

Gentlemen:

We have examined the accounts of the secretary-treasurer of the Association for Research in Ophthalmology, Inc., for the year ended December 31, 1950. In this connection we have reviewed the system of internal control and the accounting procedures of the association and have examined accounting records and other supporting evidence, by methods and to the extent we deemed appropriate. Our examination was made in accordance with generally accepted auditing standards applicable in the circumstances and included all procedures which we considered necessary, except that we did not confirm unpaid dues directly with members.

INTRODUCTION

The association was incorporated on July 20, 1936, under the laws of the state of New York. However, it had been an unincorporated group for some years earlier, operating under a constitution and related by-laws. These were embodied in the certificate of incorporation. The association has no shareholders and is exempt from federal taxes. However, it is required to file annually a federal information return reporting the source and disposition of income.

SCOPE OF EXAMINATION

Cash receipts as recorded in the cash book were traced into bank. Dues shown as paid were checked to individual membership cards. Cash from this source was reconciled to the total number of members shown on the official list which is to be furnished to individual members. A minor discrepancy was noted, consisting of one more \$2.00 educational membership paid for than was anticipated. We do not consider this a material objection.

Interest from U. S. bonds was verified by count of coupons attached. Matured coupons amounting to \$175.00, due through December 31, 1950, were found affixed. These were clipped and deposited in bank in the presence of our representative on May 16, 1951. We found no feasible means of verifying independently the amount of proceeds from banquet.

Disbursements were found to be supported by cancelled checks, receipted bills, and other data. They seemed proper.

Confirmation of balance in bank was obtained direct from the depository and was reconciled by us. We inspected the U. S. bonds.

We also examined the certificate of incorporation, constitution and by-laws, the insurance policy, minutes, and such other data as was pertinent.

GENERAL

Constitutional provisions as to bond of the secretary-treasurer and an annual audit by a certified public accountant were found to have been complied with. A federal information return for 1950 was prepared.

Although formal action in documented form did not appear to have been taken with regard to the Proctor Medal Fund, we were advised that it is the intention of the donor that the fund be kept intact and the income used to defray cost of a medal to be presented periodically for outstanding accomplishment in ophthalmology. It appeared to us that the financial provisions of this condition had been met as to the year under examination. We were further advised that it is the sense of the association that the income is to go into the general fund and that, should the income be insufficient to defray the cost, the general fund is to provide the balance.

All financial activity during the year appeared to be reflected in the accounts and all assets similarly appeared to have been recorded. We found no evidence of any debt or other commitments due by the association at December 31, 1950. In addition, we obtained from the secretary-treasurer a certificate attesting the correctness of these statements.

CERTIFICATE

In our opinion, the accompanying exhibits present fairly the fund balances of the Association for Research in Ophthalmology, Inc., as of December 31, 1950, and the total receipts and disbursements for the year then ended, in conformity with generally accepted accounting principles relating to the operation of funds, applied on a basis consistent with that of the preceding year.

Yours very truly,

RYNICKER, WOOLLEY & BATES

Exhibit A

CASH AND SECURITIES IN FUNDS AS OF DECEMBER 31, 1950

	General Fund	Proctor Medal Fund	Total
Cash in bank (Exhibit "B")	\$1,812.44	\$ 15.37	\$ 1,827.81
Securities:			
U. S. Treasury Bonds 2½%—1967-72 (at cbst)			
Owned at first of year	\$4,099.84		
Purchased during year	6,084.79		
Total Funds	<u>\$1,812.44</u>	<u>10,184.63</u>	<u>10,184.63</u>
		<u>\$10,200.00</u>	<u>\$12,012.44</u>

Exhibit B

STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS

Year Ended December 31, 1950

	General Fund	Proctor Medal Fund
Cash on hand and in bank—first of year	\$1,305.68	\$6,100.16
Add—Receipts:		
1949 Dues:		
3 Active members at \$5.00	\$ 15.00	
3 Educational members at \$2.00	6.00	21.00
1950 Dues (Schedule "B-1")		2,727.00
1951 Dues		
3 Active members at \$5.00		15.00
Banquet proceeds	300.00	
Bond interest		50.00
From Proctor Medal Fund (contra below)		50.00
Total Receipts	<u>3,113.00</u>	<u>50.00</u>
	<u>4,418.68</u>	<u>6,150.16</u>
Deduct—Disbursements:		
Convention expenses:		
Dinners	\$665.67	
Programs, mailing fees, notices	373.54	
Reporting meeting	197.95	
Expenses of Secretary-Treasurer	100.00	
Clerk and projectionist	30.00	1,367.16
Printing proceedings—1949 meeting		779.67
Stationery, supplies and printing		218.94
Auditing		91.50
Postage and express		59.38
Addressograph		30.00
Premium—\$5,000.00 position bond—Secretary-Treasurer		25.00
Bank charges and miscellaneous		21.02
Safety deposit box rental (1 year)		10.60
Purchase of \$6,000.00 face U. S. bonds		6,084.79
Transferred from Proctor Medal Fund to General Fund (contra above)		50.00
Engraving Proctor Medal		2.97
Total Disbursements	<u>2,606.24</u>	<u>6,134.79</u>
Cash in bank—end of year (to Exhibit "A")	<u>\$1,812.44</u>	<u>\$ 15.37</u>

Exhibit B-1

CHANGES IN MEMBERSHIP AND RECONCILIATION WITH DUES PAID

Year Ended December 31, 1950

<i>Changes in Membership</i>	Life	Hon- orary	Educa- tional	Active	Sus- taining	Total
<i>Membership January 1, 1950</i>	1	11	50	391	21	474
<i>Add:</i>						
Elected for 1950 membership at Fall, 1949, meeting of Board of Trustees	—	—	16	22	—	38
Elected at June, 1950, meeting of Board of Trustees	—	—	29	24	—	53
Unlocated difference	—	—	1	—	—	1
Totals	1	11	96	437	21	566
<i>Deduct:</i>						
Deceased in 1950	—	2	—	3	—	5
Resigned and retired in 1950	—	—	—	2	—	2
Memberships lapsed for non-payment of dues (1):						
Members at first of year	—	—	13	31	1	45
Members elected for 1950	—	—	4	1	—	5
Totals	—	2	17	37	1	57
	1	9	79	400	20	509
<i>Changes in Classes of Memberships:</i>						
From active to sustaining	—	—	—	(9)	9	—
From sustaining to active	—	—	—	5	(5)	—
From educational to active	—	—	(2)	2	—	—
<i>Membership December 31, 1950</i>	1	9	77	398	24	509
<i>Reconciliation with Dues Paid</i>						
<i>Dues for 1950 paid in 1949</i>	—	—	1	3	—	4
<i>Dues paid in 1950:</i>						
Life and honorary	\$ waived	1	9	—	—	10
Educational at \$2.00	152.00	—	76	—	—	76
Active at \$5.00	1,975.00	—	—	395	—	395
Sustaining at \$25.00	600.00	—	—	—	24	24
To Exhibit "B"	\$2,727.00	1	9	77	398	509

Note: (1) Under the constitution, dues must be paid to obtain educational, active or sustaining membership.

Exhibit C

SUMMARY OF MEMBERSHIP BY YEARS
TO DECEMBER 31, 1950

Years Ended Dec. 31:	Total Members		
1950 (Schedule "B-1")	(1) 509	1939	268
1949	(1) 474	1938	272
1948	422	1937	249
1947	306	1936	240
1946	324	1935	245
1945	(2) —	1934	230
1944	283	1933	219
1943	(2) —	1932	203
1942	281	1931	193
1941	279	1930	134
1940	270		

Notes: (1) Excludes dues-paying memberships lapsed for non-payment.

(2) Not available, due to wartime dislocation.

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

December 31, 1951

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 Graham, John H.
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 Jacoby, Mark W.
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